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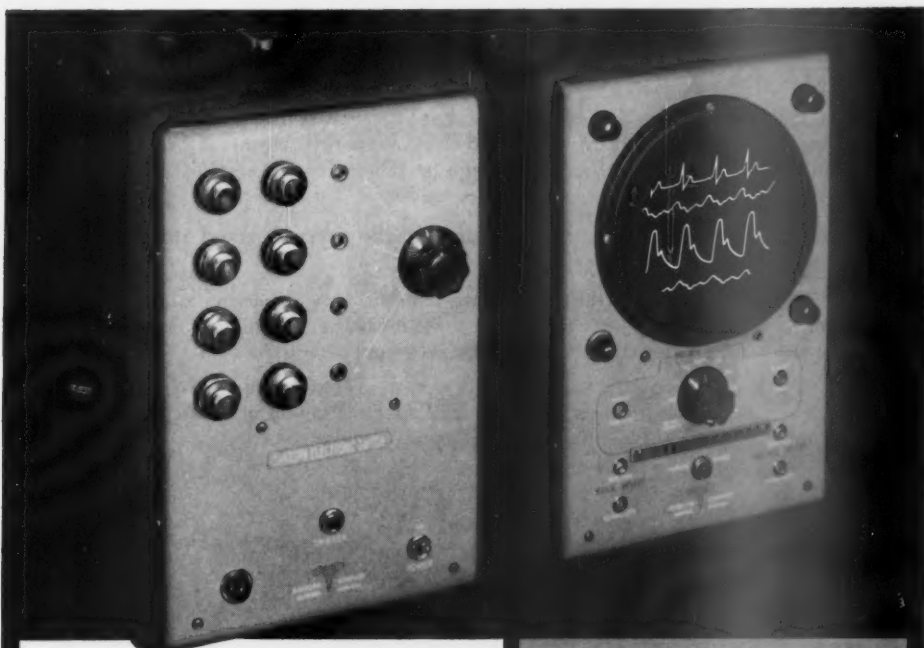
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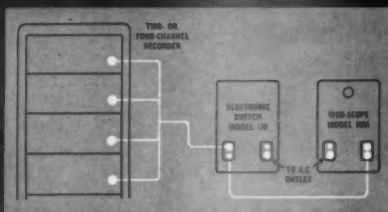


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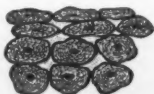


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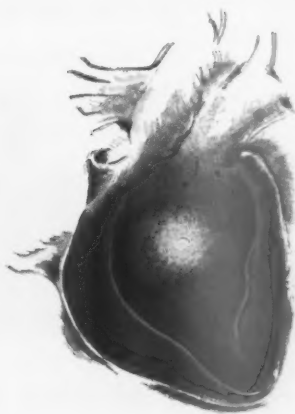
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1. American Heart Association: Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, Charles H. Rammelkamp, Chairman: *Circulation* 15:154 (Jan.) 1957.



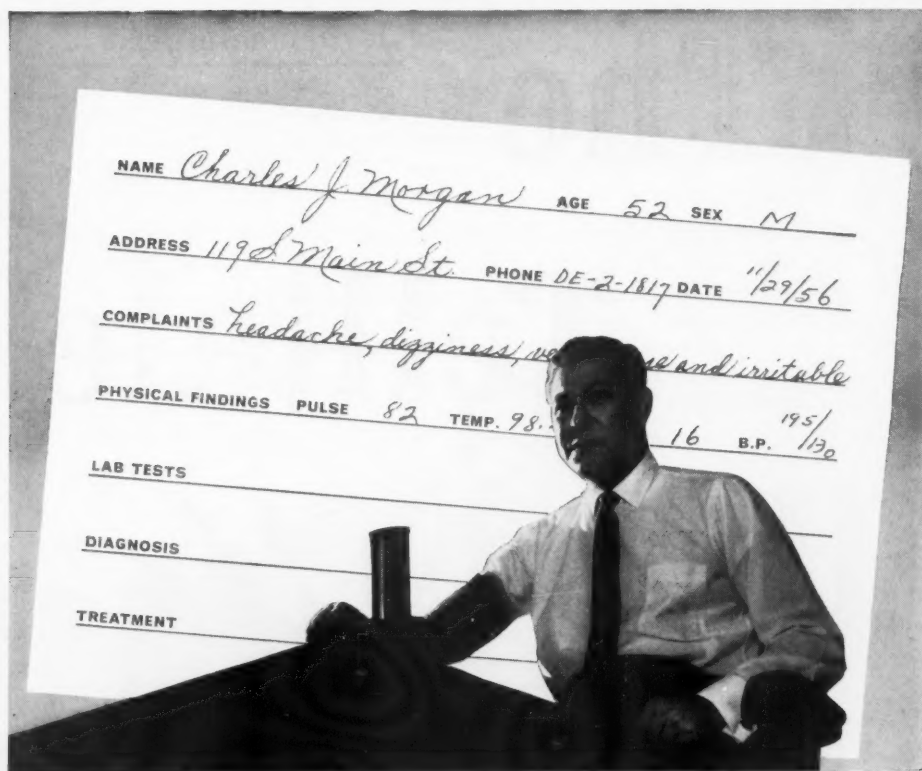
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1. LaBarbera, J.F.: Med. Rec. & Ann. 50:242, 1956. 2. Ledbetter, P.V., and Morrow, E.J.: J. Am. Geriatrics Soc. 3:172 (March) 1955. 3. Wilkins, R.W.: Am. J. Med. 17:703 (Nov.) 1954. 4. Moyer, J.H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. 96:530, 1955.

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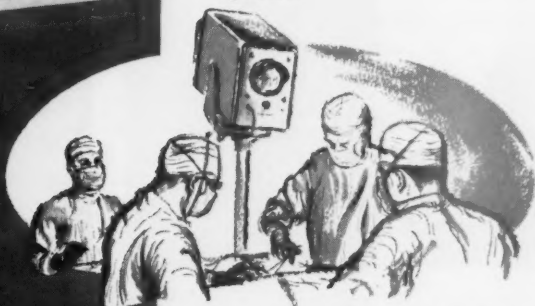
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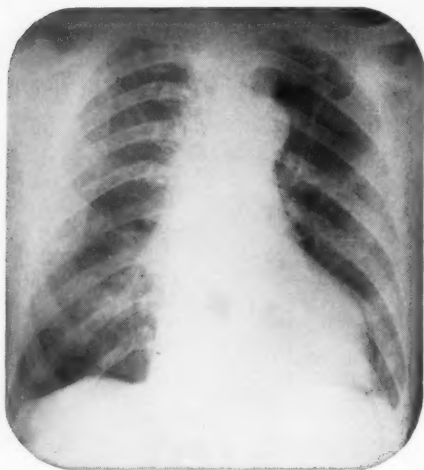
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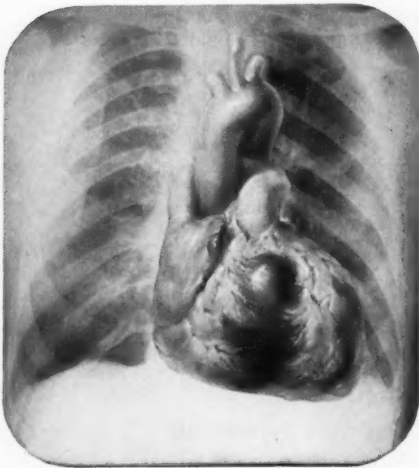
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For resistant rheumatics, Buffered Pabirin AC Tablets provide the added benefits of hydrocortisone. Acetylsalicylic acid reduces corticoid dosage and minimizes the risk of adrenal atrophy.

And PABA retards breakdown of hydrocortisone by the liver, thereby prolonging the effect of small doses.

Buffered Pabirin and Buffered Pabirin AC Tablets are both sodium and potassium free.

for most rheumatoid arthritics

Buffered **Pabirin®**
TABLETS

300 mg.	Hydrocortisone
300 mg.	Acetylsalicylic acid (5 gr.)
50 mg.	Para-aminobenzoic acid (5 gr.)
100 mg.	Ascorbic acid
	Dried aluminum hydroxide gel

for resistant rheumatics

Buffered **Pabirin® AC**
TABLETS

2.5 mg.
300 mg.
300 mg.
50 mg.
100 mg.

SMITH-DORSEY • Lincoln, Nebraska • a division of The Wander Company

HOW TANDEM RELEASE TABLETS WORK

The outer layer of Buffered Pabirin Tablets quickly releases aluminum hydroxide for buffering action. PABA to potentiate acetylsalicylic acid and therapeutic doses of ascorbic acid to offset depletion are also in the outer layer.

After the buffering action has started, the inner core of Buffered Pabirin Tablets, containing acetylsalicylic acid, begins to expand.

The inner core then disintegrates rapidly and permits fast absorption of the acetylsalicylic acid.

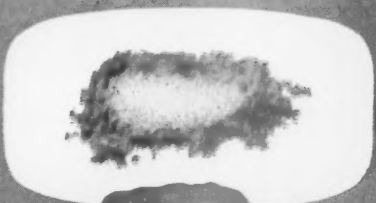
Buffered Pabirin AC Tablets release, in addition, hydrocortisone from the core.



2-STAGE DISINTEGRATION



IN MINUTES



Buffered Pabirin Tablets

Dosage: Two or three tablets 3 or 4 times daily. In rheumatic fever three to five tablets 4 or 5 times daily.

Buffered Pabirin AC Tablets

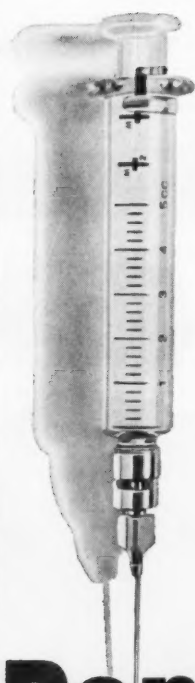
Dosage: Initially, one or two tablets 4 times daily, after meals and on retiring. Reduction of dosage should be gradual; never stop therapy abruptly.



RESULTS:

- increased range of motion
- faster pain relief

**only
one
injection
a
month**



Percorten[®]

trimethylacetate

(desoxycorticosterone trimethylacetate CIBA)

controls adrenocortical insufficiency

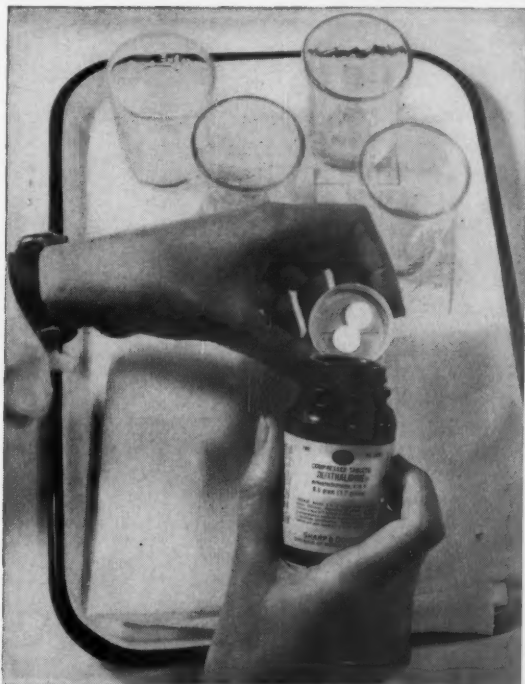
One monthly injection of Percorten affords prolonged, well-regulated hormone therapy for patients with Addison's and other diseases marked by adrenocortical insufficiency...

- **without** annoying and painful daily injections
- **without** unpleasant implantation of pellets

Multiple-dose Vials, 4 ml., each ml. containing 25 mg. Percorten trimethylacetate as an aqueous microcrystalline suspension for intramuscular use only.

C I B A
SUMMIT, N. J.

2/238549



A good start for safer bowel surgery



PHTHALYLSULFATHIAZOLE

The virtual "sterilization" of pathogenic bowel contents which follows preoperative administration of **SULFATHALIDINE** eliminates a major danger in intestinal surgery. Postoperatively, **SULFATHALIDINE** continues the suppression of dangerous pathogens, lessens the likelihood of peritonitis and abscess formation. Flatus is minimal; fungi and yeast do not overgrow their habitat; early healing is promoted. **SULFATHALIDINE** is an important adjunct in ulcerative colitis.

CREMOTHALIDINE® is a palatable suspension of **SULFATHALIDINE**. Each 30 cc. (1 fluidounce) contains 6.0 Gm. **SULFATHALIDINE**.



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DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

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Direct, fast relief of **gi** and pain: **Bentyl**

ga
spasm

Relieves the pain where it hurts: the gut

2 caps t.i.d.

J. Hardin, J. H. Levy, J. S., and Seager, L. South. M. J. 47:1190-1954

THE WM. S. MERRELL COMPANY • New York • CINCINNATI • St. Thomas, Ontario

TRADE MARK "BENTYL"


Merrell
Since 1828

In the anemia of pregnancy....

"The combined use of iron and cobalt [Roncovite] produces better clinical results, apparently by maintaining normal marrow function and by supplying adequate amounts of iron."*

*Holly, R. G.: Iron and Cobalt in Pregnancy, *Obst. & Gynec.* (Mar.) 1957.

IN PREGNANCY, AS IN ALL IRON DEFICIENCY
ANEMIAS, THE BIBLIOGRAPHY SPECIFIES

RONCOVITE®

Lloyd Brothers, Inc. • Cincinnati, 3, Ohio

HYPERTENSION

"ACTING IN CONCERT"†

to treat
the hypertensive patient
as a whole

Unitensen-R combines cryptenamine and reserpine which "act in concert" to control the entire syndrome of essential hypertension.

Cryptenamine dependably lowers blood pressure, and improves cerebral and renal circulation. It also increases cardiac efficiency, and may arrest the progress of vascular damage.

Reserpine raises the threshold of emotional response and stifles neurogenic aggravation of the disease.

Given together, cryptenamine and reserpine produce a far better therapeutic effect than when given separately. And successful therapy is usually maintained with dosages well below those producing side effects.

†Cohen, B. M.; Cross, E. B., and Johnson W.: Am. Prac. & Digest Treat. 6: 1030, 1955.

UNITENSEN[®]-R

U.S. Pat. 2,811,111

IRWIN, NEISLER & COMPANY
DECATUR, ILLINOIS

Each grey-coated Unitensen-R tablet contains:

Cryptenamine.....1.0 mg.
(tannates)

Reserpine.....0.1 mg.

Dosage: 1 tablet t.i.d.

For prescription economy,
prescribe in 50's.

To serve your patients today—
call your pharmacist for any additional information you may need to help you prescribe Unitensen-R.

Bibliography. Orgain, E. S.: Postgrad. Med. 17:318, 1955. Finnerty, F. A.: Am. J. Med. 17: 629, 1954. McCall, M. L.; Saxe, D. K.; Wagstaff, C., and Cutler, J.: Obst. & Gynec. 6: 297, 1955. Cohen, B. M.: New York State J. Med. 55: 653, 1955. LaBarbera, J. F.: Med. Record and Annals 50: 242, 1956. Voskian, J.; Assali, N. S., and Noll, L.: Surg., Gynec. & Obst. 102: 37, 1956. Crisp, W. E., and McCall, M. L.: Am. Prac. & Digest Treat. 7: 620, 1956. Finnerty, F. A.: Am. J. Med. Sc. 229: 379, 1955.



Hypertensive Objective:

ACTIVE LIVING

... from incapacitating hypertension to a life of usefulness.

Case History:¹ A.B., 42-year-old hospitalized patient with severe hypertension and early heart failure. Blood pressure prior to treatment was 240/160 mm. Hg. ANSOLYSEN was administered orally t.i.d. The dose was adjusted to the patient's requirements. Blood pressure was reduced to, and stabilized at, an average level of 150/105 mm. Hg. There was marked symptomatic improvement, and the patient was able to return to work.

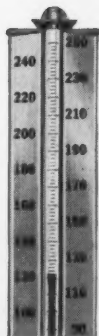
1. Case history on file in Medical Department of Wyeth Laboratories.

ANSOLYSEN[®]

TARTRATE

Pentolinium Tartrate

Lowers Blood Pressure



Philadelphia 1, Pa.

thousands of physicians
confirm daily in practice
the overwhelming evidence
in hundreds of publications

METICORTEN[®]

prednisone

overwhelmingly favored by physicians in rheumatoid arthritis and bronchial asthma

increasingly favored by physicians in intractable hay fever, nephrosis, disseminated lupus erythematosus and acute rheumatic fever

METICORTEN, 1, 2.5 and 5 mg. white tablets.

MC-J-347

Schering



AMERICAN STOMACH

- Acid distress
- Heartburn
- Dyspepsia
- Peptic ulcer

For the hyperacidity that is so common on the American scene, ALUDROX gives acid-hungry therapeutic action without systemic penalties. ALUDROX combines reactive alumina gel with milk of magnesia in a rational proportion of 4:1. It is a balanced formula for prompt relief, soothing action, and healing powers—without constipation, acid rebound, or alkalosis.

TABLETS

SUSPENSION

ALUDROX®

Aluminum Hydroxide with Magnesium Hydroxide
to neutralize, not penalize



Philadelphia 1, Pa.



you
can
police
overweight
patients

When ardent persuasion is not enough...

to maintain patients on a prescribed diet until conditioned to lower food intake, assign REVICAPS to police their appetite.

REVICAPS encourage dietary discipline by safely curbing appetite as well as hunger contractions during the initial difficult period of weight reduction.

REVICAPS combine all three accepted adjuncts to reducing diets: d-amphetamine, methylcellulose, vitamins and minerals.

Include REVICAPS in the reducing regimen you prescribe.

Available on Prescription Only



REVICAPS* accepted
reducing
medication

d-Amphetamine-Methylcellulose-Vitamins and Minerals

Dosage: 1 or 2 capsules $\frac{1}{2}$ to 1 hour before meals.



LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

* REG. U. S. PAT. OFF.

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Why are **PERCODAN**[®] Tablets better for pain?

SPEED OF ACTION	WITHIN 5-15 MINUTES ¹⁻³	almost immediate relief of pain
DURATION OF EFFECT	6 HOURS AND LONGER ¹⁻³	sleep uninterrupted by pain
THOROUGHNESS OF PAIN RELIEF	USUALLY COMPLETE ¹⁻⁵	reliability of pain relief
INCIDENCE OF CONSTIPATION	RARE ¹⁻³	excellent for chronic and bedridden patients

Better than codeine plus APC¹⁻⁵

Average adult dose: 1 PERCODAN[®] Tablet every 6 hours.

Supplied: Scored, yellow oral tablets, containing salts of dihydrocodeinone and homatropine, plus APC. May be habit-forming. PERCODAN Tablets are available at all pharmacies.

References: 1. Piper, C. E., and Nicklas, F. W.: *Indust. Med.* 23:510, 1954. 2. Blank, P., and Boas, H.: *Ann. West. Med. & Surg.* 6:376, 1952. 3. Chasko, W. J.: *J. District of Columbia Dent. Soc.* 31:3, No. 5, 1956. 4. Cass, L. J., and Frederick, W. S.: *M. Times* 84:1318, 1956. 5. Bonica, J. J.: *GP* 10:35, No. 5, 1954.

Literature? write



ENDO LABORATORIES, Richmond Hill 19, New York

[®]U. S. Pat. 2,628,195

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each dose is fresh
...for complete potency

FOLBESYN^{*}

VITAMINS **LEDERLE**
B COMPLEX + C

Separate packaging of dry vitamins and diluent (mixed immediately before injection) assure controlled dosage. The folic acid solution is specially prepared to preserve full potency and to serve for quick solution of the dried vitamins. FOLBESYN may be conveniently added to standard intravenous solutions.

Dosage: 2 cc. daily.



Each 2 cc. dose contains:

Thiamine HCl (B ₁)	10 mg.
Riboflavin (B ₂)	10 mg.
Niacinamide	50 mg.
Pyridoxine HCl (B ₆)	5 mg.
Sodium Pantothenate	10 mg.
Ascorbic Acid (C)	300 mg.
Folic Acid	5 mg.
Vitamin B ₁₂	15 mcgm.



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*REG. U. S. PAT. OFF.

a longer lease on life
for hypertensives

VASCUTUM[®]

with Quercetin improved

Hypertension associated with capillary fault induces a mortality rate 815% higher than that found in normotensives. Quercetin can reduce this excessive rate by as much as 76%.*

When hypercholesterolemia is a complicating factor in degenerative disease, the hypotency lipotropes in Vascutum have been shown to produce a significant reduction in this mortality rate.†

VASCUTUM improved

Each Capsule contains:

Choline bitartrate	200 mg.
Inositol tartrate	100 mg.
β- Methionine	24 mg.
Pyridoxine HCl	0.57 mg.
Quercetin	15 mg.
Ascorbic Acid	100 mg.
Thiamin HCl	2 mg.

Supplied in bottles of 100 and 500 capsules.

Suggested dosage: One Capsule 3 or 4 times daily.

VASCUTUM is the REGISTERED TRADEMARK OF SCHENLEY LABORATORIES, INC., FOR THE LIPOTROPIC-ANTIHYPERTENSIVE PRODUCT.

†G. Griffith, J. Q. J., et al., *Ann. Int. Med.* 1955, 42, 1712.
 ‡G. Griffith, J. Q. J., et al., *Ann. Int. Med.* 1955, 42, 1712.
 Med. Clin. North America, November, 1955, p. 1712.



SCHENLEY LABORATORIES, INC.



for relief of daily tensions...

"...a calmative effect...superior to anything we
had previously seen with the new drugs."*

true calmative

nostyn[®]

Ectylurea, AMES
(2-ethyl-cis-crotonylurea)

the power of gentleness

*allays anxiety and tension
without depression, drowsiness, motor incoordination*

NOSTYN is a *calmative*—not a hypnotic-sedative—unrelated to any available chemopsychotherapeutic agent • no evidence of cumulation or habituation • does not increase gastric acidity or motility • unusually wide margin of safety —no significant side effects

dosage: 150-300 mg. (½ to 1 tablet) three or four times daily.

supplied: 300 mg. scored tablets, bottles of 48 and 500.

*Ferguson, J. T., and Linn, F. V. Z.: *Antibiotic Med. & Clin. Therapy* 3:329, 1956.



AMES COMPANY, INC • ELKHART, INDIANA

AMES COMPANY OF CANADA, LTD., TORONTO

28097

NEW HYDELTRA®-T.B.A.

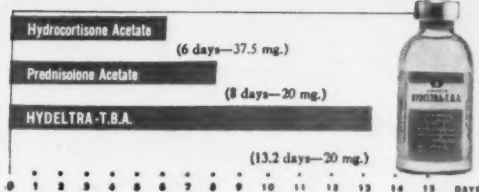
(Prednisolone tertiary-butylacetate, Merck)

for relief that lasts—longer

in *COLLATERAL*
LIGAMENT
STRAINS—
allows early
ambulation—
relieves pain
and swelling

Rheumatoid arthritis
Osteoarthritis
Acute gouty arthritis
Bursitis
Sprains
Tendinitis
Trigger finger
Peritendinitis
Trigger points
Tennis elbow
Lumbosacral strain
Capsulitis
Frozen shoulder
Coccydynia
Rheumatoid nodules
Fibrositis
Tensor fascia lata
syndrome
Collateral ligament
sprains
Radiculitis
Osteochondritis
Ganglia

Duration of relief
exceeds that
provided by any
other steroid
ester



Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone tertiary-butylacetate, in 5-cc. vials.



MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

severe asthma

*is usually aggravated
and prolonged
by a strong emotional overlay*

In one study, 'Thorazine'
relaxed and improved 11 of
12 patients within one hour
after injection . . . in one case
"appeared to be life-saving."¹

'Thorazine' promptly alleviates the emotional
stress which may precipitate, aggravate or
prolong an asthmatic attack. It enables the patient
to sleep, yet does not depress respiration.

Available: Ampuls, Tablets, Syrup (as the
hydrochloride), and Suppositories (as the base).

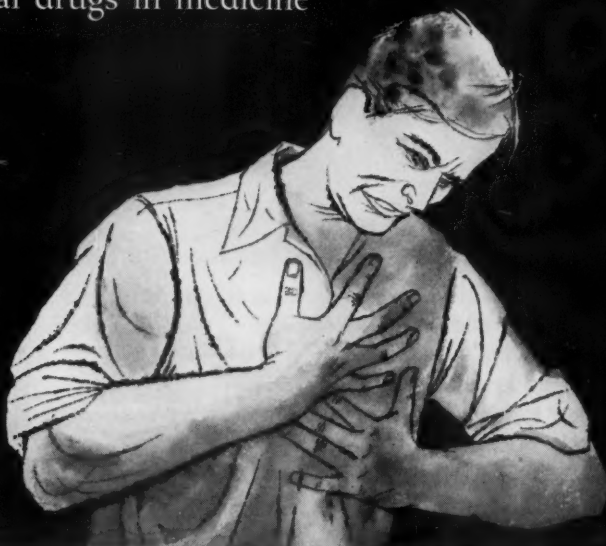
Smith, Kline & French Laboratories, Philadelphia

1. Ende, M.: Am. Pract. & Dig. Treat. 6:710 (May) 1955.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

THORAZINE*

one of the fundamental drugs in medicine



relaxes both mind and muscle

*for anxiety
and tension in
everyday practice*

- well suited for prolonged therapy
- well tolerated, relatively nontoxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to phenothiazine compounds and rauwolfia derivatives
- orally effective within 30 minutes for a period of 6 hours

For treatment of **anxiety and tension states and muscle spasm**

Miltown®

THE ORIGINAL MEPROBAMATE

2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U. S. Patent 2,724,720
Tranquilizer with muscle-relaxant action

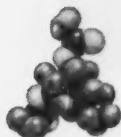
DISCOVERED AND INTRODUCED

BY  WALLACE LABORATORIES, New Brunswick, N. J.

SUPPLIED: (Bottles 50 tablets)
400 mg. scored tablets
200 mg. sugar-coated tablets

USUAL DOSAGE: One or two 400 mg. tablets t.i.d.

Literature and Samples Available on Request



THE MILTOWN®
MEPROBAMATE MOLECULE



CH-3707-RS

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A brighter outlook comes with a "sense of well-being"



Every woman who suffers in the menopause deserves "Premarin."

"Premarin" provides prompt relief from distressing symptoms and an added "sense of well-being."

"Premarin," available as tablets and liquid, presents the complete equine estrogen-complex. Has no odor, imparts no odor.

"PREMARIN"®
Conjugated estrogens (equine)

in the menopause and
the pre-and postmenopausal syndrome



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new

Gantrimycin

two different antibacterial actions:

the action of
a single, soluble sulfonamide
plus the antibiotic action
of oleandomycin

Why? →

Gantrimycin

Gantrimycin is Gantrisin plus oleandomycin --
a tablet within a tablet.

Gantrimycin is effective against many infections refractory to other antibiotics because Gantrisin interferes with the basic nutrition of the pathogens, and oleandomycin attacks another vital system in the growth and reproduction of the pathogens.

Gantrimycin acts against the great majority of common pathogens and provides more certainty of therapeutic success -- particularly in:

- . Upper and lower respiratory tract infections
- . Pyogenic infections
- . Urinary infections

Gantrimycin is well tolerated. No danger of renal blocking. No need for alkalies or forced fluids.

Each Gantrimycin tablet contains 333 mg Gantrisin® (brand of sulfisoxazole) and 75 mg oleandomycin (as the phosphate salt). Available in bottles of 50 tablets.

Hoffmann - La Roche Inc • Nutley • N. J.

Rauwiloid®

A Better Antihypertensive

"We prefer to use alseroxylon (Rauwiloid)

since it is less likely to produce excessive fatigue and weakness than does reserpine."¹ Up to 80% of patients with mild labile hypertension and many with more severe forms are controlled with Rauwiloid alone.

1. Moyer, J.H.: J. Louisiana M. Soc.
108:231 (July) 1956.

A Better Tranquilizer, too

"...relief from anxiety resulted in generally increased intellectual and psychomotor efficiency with a few exceptions."² Rauwiloid is outstanding for its *nonsoporific* sedative action in a long list of unrelated diseases not necessarily associated with hypertension but burdened by psychic overlay.

2. Wright, W.T., Jr., et al.: J. Kansas M. Soc.
57:410 (July) 1956.

Dosage: Merely two 2 mg. tablets at bedtime.
After full effect one tablet suffices.

Best first step when more potent drugs are needed

Rauwiloid is recognized as basal medication in all grades and types of hypertension. In combination with more potent agents it proves synergistic or potentiating, making smaller dosage effective and freer from side actions.

Rauwiloid® + Veriloid®

In moderate to severe hypertension this single-tablet combination permits long-term therapy with dependably stable response. Each tablet contains 1 mg. Rauwiloid (alseroxylon) and 3 mg. Veriloid (alkaverir). Initial dose, 1 tablet t.i.d., p.c.

Rauwiloid® + Hexamethonium

In severe, otherwise intractable hypertension this single-tablet combination provides smoother, less erratic response to hexamethonium. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate. Initial dose, ½ tablet q.i.d.

Riker LOS ANGELES



*"You say you can also mix
it with flavorful orange
or luscious grape juice?"*

It is hard to decide which is best . . .
Metamucil with water, milk or fruit
juice—they combine equally well with
Metamucil. But use *cool* liquid for best
results. Irritant laxatives are unnecessary
with Metamucil since this hydrophilic
mucilloid produces soft, easy stools *and*
stimulates normal peristalsis.

METAMUCIL® **SEARLE**

psyllium hydrophilic mucilloid with dextrose

KNOX PROTEIN PREVIEWS

Overcoming Today's No. 1 Nutritional Problem



Knox "Choice of Foods" Diet Can Help Your HYPERTENSIVE Patients to Reduce and Stay Reduced



1. Color coded diets of 1200, 1600 and 1800 calories are based on nutritionally tested Food Exchanges.¹

2. The easy-to-use Food Exchanges (called Choices in booklet) simplify diet management by eliminating calorie counting.

3. Diets promote accurate adjustment of caloric levels to the special needs of the patient yet allow each individual considerable latitude in the choice of foods.

4. More than six dozen appetizing, low-calorie recipes are described in the last fourteen pages of the diet booklet.

1. The Food Exchange Lists referred to are based on material in "Meal Planning with Exchange Lists" prepared by Committees of the American Diabetes Association, Inc., and The American Dietetic Association in cooperation with the Chronic Disease Program, Public Health Service, Department of Health, Education and Welfare.

Chas. B. Knox Gelatine Co., Inc.
Professional Service Dept. AI-3
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Please send me dozen copies of the new, illustrated Knox Reducing booklet based on Food Exchanges.

Your Name and Address,

Your Rx of Sustagen Feedings q.2h.

buffers acid
builds tissue
accelerates healing
provides a bland high protein diet

Sustagen®

PROVIDES FOOD FOR THE PATIENT
PROVIDES THERAPY FOR THE LESION



**a peptic ulcer patient ...
comfortable...well fed...on the job!**

MEAD JOHNSON

SYMBOL OF SERVICE IN MEDICINE

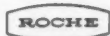
Gentle

is the word
for Noludar

Mild, yet positive in action, Noludar 'Roche' is especially suited for the tense patient who needs to relax and remain clear-headed—or for the insomniac who wants a refreshing night's sleep without hangover. Not a barbiturate, not habit-forming. Tablets, 50 and 200 mg; elixir, 50 mg per teasp.



Noludar® brand of methyprylon
(3,3-diethyl-5-methyl-
2,4-piperidinedione)



Original Research in
Medicine and Chemistry

*Three essential steps
in establishing correct
eating patterns:*

**SUPERVISION
BY THE
PHYSICIAN^{1,2,3}**

1

**A BALANCED
EATING PLAN^{1,2,3}**

2

In the development and maintenance of good eating habits, there are three essentials: support and supervision by the physician, a balanced eating plan, and selective medication.^{1,2,3}

**SELECTIVE
MEDICATION^{1,2,3}**

3

OBEDRIN PROVIDES:

- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B₁ and B₂ plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Since Obedrin contains no artificial bulk, the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat. 5:778 (Oct. 1954).
2. Freed, S.C.: G.P. 7:63 (1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb. 1954).

Obedrin[®]

and the 60-10-70 Basic Plan

FORMULA:

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine mononitrate 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

Write for 60-10-70 Menu pads, weight charts and clinical supply of Obedrin.

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE

NEW YORK

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KANSAS CITY

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SAN FRANCISCO

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Conditions requiring diuretic treatment

for sustained periods of time can be ideally controlled by DIAMOX.

DIAMOX has been found strikingly effective in a variety of conditions: cardiac edema, glaucoma, epilepsy, toxemias of pregnancy, obesity, premenstrual tension.

Administration of DIAMOX once daily or every other day results in adequate control of edema since DIAMOX is effective in the **mobilization** of edema fluid and in the **prevention of fluid accumulation**.

A versatile diuretic, DIAMOX is well-tolerated orally, and even when given in long term dosage, side effects are rare. Excretion by the kidney is usually complete within 12 hours with no cumulative effects.

Dosage can be adjusted to ensure a restful night.

Supplied: Scored tablets of 250 mg. (Also in ampuls of 500 mg. for parenteral use.)

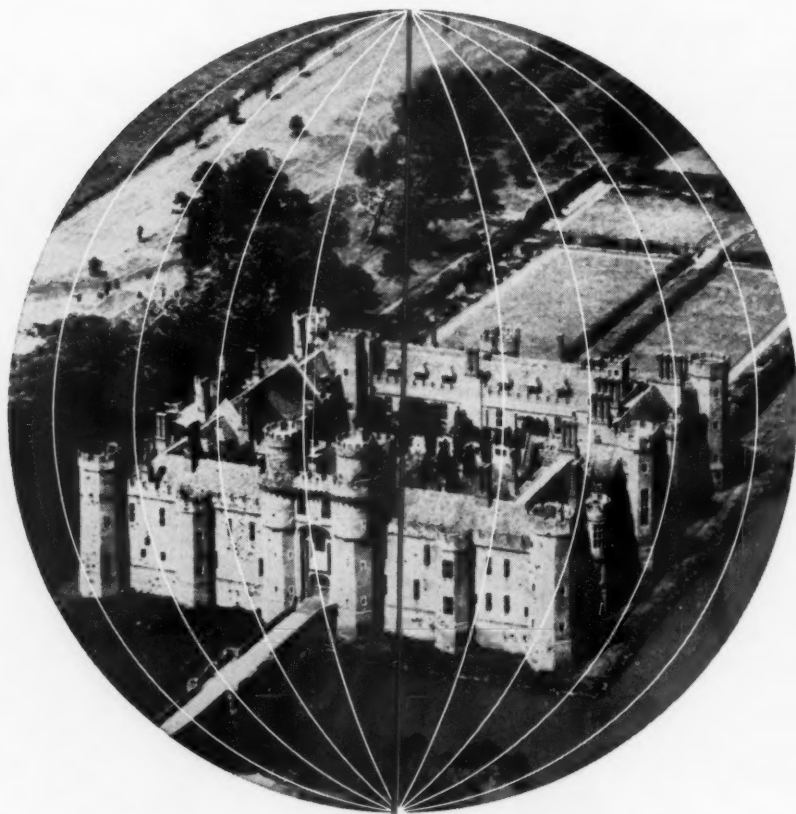
Diamox*

nonmercurial diuretic

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY,
2700 H.P. Rd. 68, EAST RUTHERFORD, N.J. 07073

Lederle

ESTABLISHED STANDARD



In medical science . . .

Penicillin continues to hold
its prime position.

It remains the accepted standard—
the antibiotic of choice in
approximately 72% of infectious disease.

Whenever oral penicillin is indicated—
oral BICILLIN sets a standard.

Its clinical dependability is assured
through resistance to gastric
destruction and optimal absorption.

*The Greenwich Observatory marks
the prime meridian of the earth.
All time and space concepts of
the globe are standardized from
that point.*



Philadelphia 1, Pa.

TABLETS

SUSPENSION

BICILLIN®

Benzathine Penicillin G
(Dibenzylethylenediamine Dipenicillin G)

penicillin with a surety factor

Please Mention this Journal when writing to Advertisers

"a safe and reliable soporific and sedative"¹



Medomin®

(heptabarbital GEIGY)

Effective Hypnosis With ordinary hypnotic dosage of 200 mg., 90 per cent of patients achieve sleep within the hour, lasting generally throughout the night.¹ Compared with other barbiturates, a notable absence of hangover or other side effects has been recorded.¹⁻³

The therapeutic ratio of MEDOMIN is unusually wide, as demonstrated both in the laboratory⁴ and in the clinic.³

Reliable Sedation MEDOMIN calms the tense and anxious patient more effectively than phenobarbital¹ and is "...particularly beneficial...in patients who exhibit anxiety or mild restlessness."²

Dosage: Hypnotic: One or two 200 mg. tablets one hour before bedtime.
Sedative: One 50 mg. or 100 mg. tablet two or three times daily.

- (1) Bauer, H. G., and Reckendorf, H. K.: A Study of the Soporific and Sedative Effectiveness of a Cycloheptenyl-ethylbarbiturate, *New York State J. Med.*, to be published.
(2) Brusca, D. D.: Clinical Study of Cycloheptenyl-ethylbarbiturate (Medomin) for Insomnia, *J. Nerv. & Ment. Dis.* 121:67, 1955. (3) Fazekas, J. F., and Koppanyi, T.: The Effects of Cycloheptenylethyl Barbituric Acid (Medomin) in Man, to be published.
(4) Koppanyi, T.; Morgan, C. F., and Princiotto, J. V.: Essential Elimination of Sodium Cycloheptenyl-ethylbarbiturate (Medomin) in Rabbits, *J. Am. Pharm. A. (Scient. Ed.)* 44:221, 1955.

MEDOMIN® (heptabarbital GEIGY). Scored tablets of 50 mg. (pink), 100 mg. (yellow) and 200 mg. (white).



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	May				June			
	6-10	13-17	20-24	27-31	3-7	10-14	17-21	24-28
The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees for all courses will be: Members, \$30.00; Non-members, \$60.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.								
Course No. 3, INTERNAL MEDICINE: The University of Chicago Department of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director, and Robert G. Page, M.D., Co-director.		X			A.M.A. Annual Meeting, New York, N. Y.			
Course No. 4, EARLY DETECTION AND PREVENTION OF DISEASE: University of Pennsylvania School of Medicine, Department of Public Health and Preventive Medicine, Philadelphia, Pa.; John P. Hubbard, M.D., F.A.C.P., and Norbert J. Roberts, M.D., F.A.C.P., Co-directors.			X					
Course No. 5, INTERNAL MEDICINE: Louisiana State University School of Medicine, Postgraduate Division, Shreveport, La.; Edgar Hull, M.D., F.A.C.P., and Marion D. Hargrove, M.D., F.A.C.P., Co-directors.			X					
Course No. 6, CARDIOLOGY: The National Institute of Cardiology of Mexico, Mexico, D. F.; Ignacio Chávez, M.D., F.A.C.P., Director.				X				
Course No. 7, INTERNAL MEDICINE: New York University Post-Graduate Medical School, New York, N. Y.; Charles F. Wilkinson, Jr., M.D., F.A.C.P., and Clarence E. de la Chapelle, M.D., F.A.C.P., Co-directors.				X				
Course No. 8, BALLISTOCARDIOGRAPHY: University of Pennsylvania School of Medicine, Philadelphia, Pa.; Isaac Starr, M.D., Director.					10-12			



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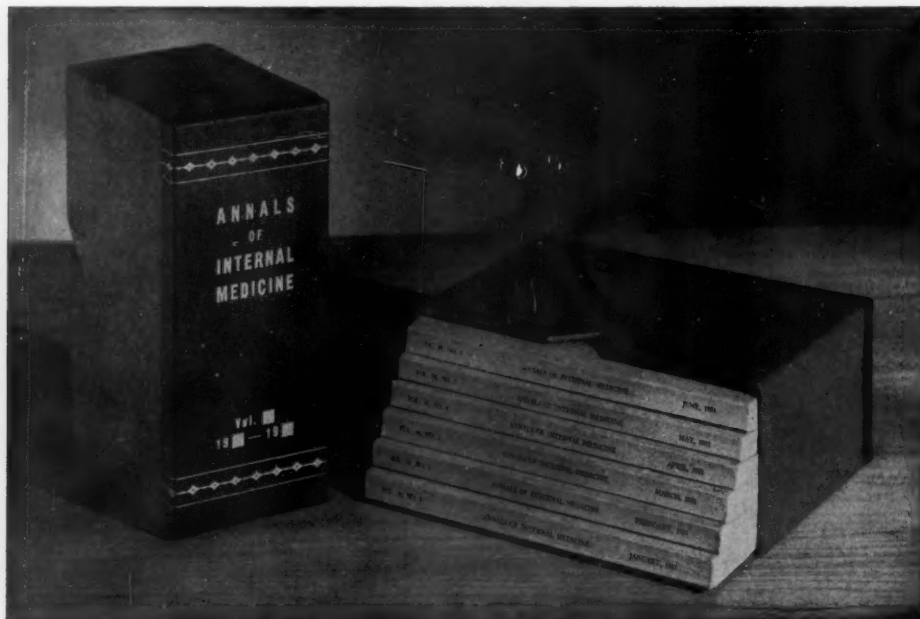
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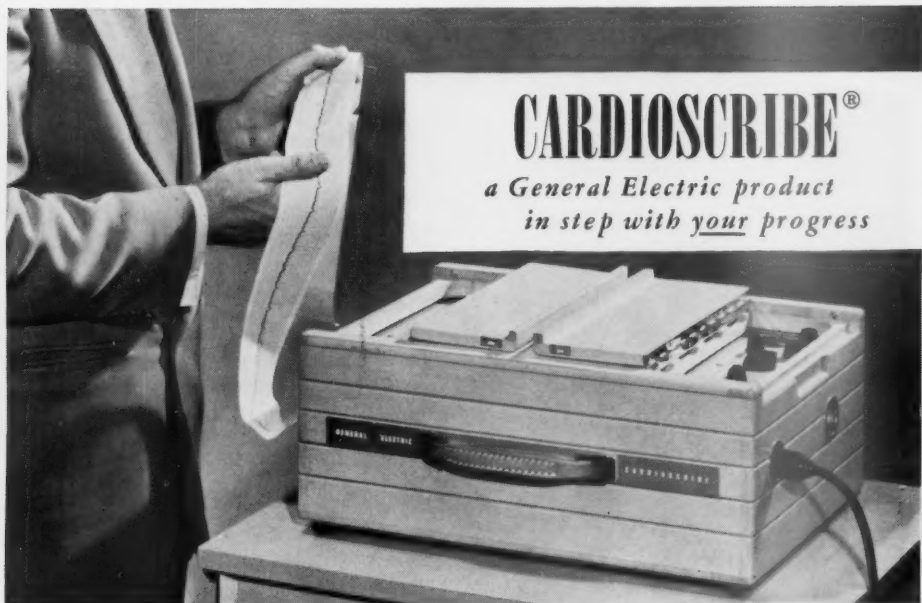
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Therapeutic benefits of MEPROLONE compared with traditional antiarthritics.

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¹ Meprobamate is the only tranquilizer with muscle-relaxant action.					

arthritis, bursitis, synovitis, tenosynovitis, myositis, fibrositis, fibromyositis, neuritis, acute and chronic low back pain, acute and chronic primary and secondary fibrositis and torticollis, intractable asthma, respiratory allergies, allergic and inflammatory eye and skin disorders (as maintenance therapy in disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma).

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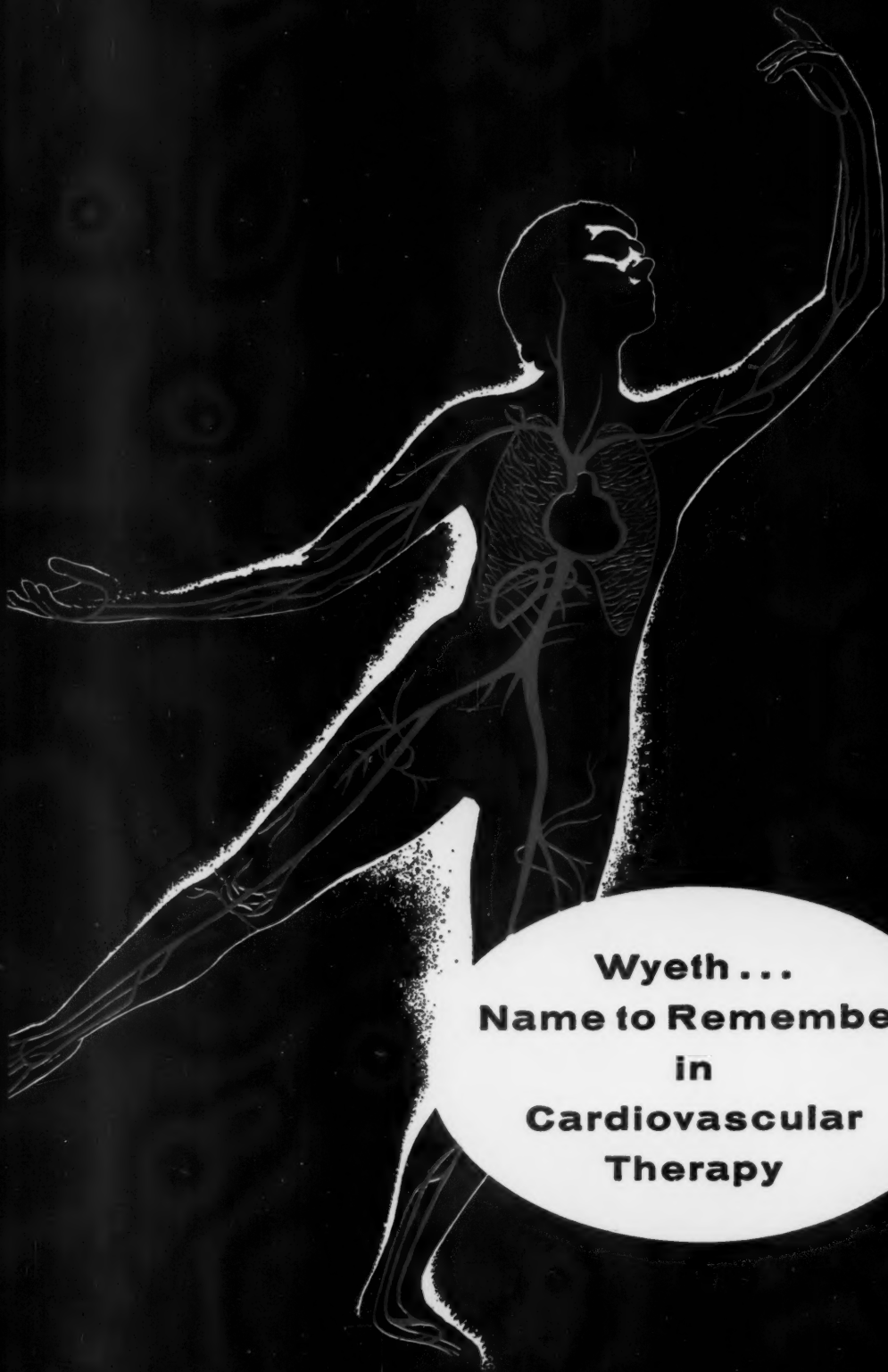
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protects your patients against the monilial
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Each capsule contains tetracycline phosphate complex equivalent to 250 mg. tetracycline hydrochloride and 250,000 units Mycostatin.

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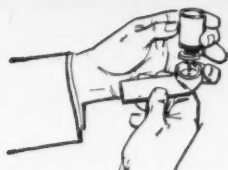
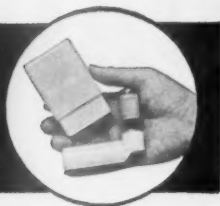
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*have been aborted faster...more effectively...
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SIMPLE TO USE



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SUITABLE
FOR CHILDREN, TOO



SLIPS INTO POCKET
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Automatically measured dosage and true nebulization...nothing to pour or measure...One inhalation usually gives prompt relief of acute or recurring asthmatic attacks.

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Medihaler-EPI® Riker brand epinephrine U.S.P. 0.5% solution in inert, nontoxic aerosol vehicle. Each measured dose 0.12 mg. epinephrine. In 10 cc. bottle with measured-dose valve.

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- reduces rigidity and tremor.
- seldom causes dryness of the mouth,
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OF PELVIC SYMPTOMS—
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REFERRED PAIN
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UPPER THIGHS;
SUPRAPUBIC PAIN**

These symptoms are frequently due to an unsuspected urethritis, which yields quickly to **FURACIN Urethral Suppositories**. Insertion of these suppositories provides gentle dilation; the anesthetic, dipiperodon, affords prompt and sustained relief of pain. The antibacterial, **FURACIN**, achieves wide-spectrum bactericidal action without tissue toxicity. Indicated for bacterial urethritis, and for topical anesthesia and prophylaxis of infection before and after instrumentation. Each suppository contains **FURACIN** 0.2% and 2% dipiperodon • HCl in a water-dispersible base. Hermetically sealed, box of 12.

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BRAND OF NITROFURAZONE suppositories

Also available: **FURACIN VAGINAL SUPPOSITORIES**



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And—while we're stretching a point—what about all those folks who choose one kind of dish, stick with it, eat it all day, every day . . . only to discover (to their chagrin) that they've shortchanged themselves nutritionally? Especially in the important B-complex vitamins. So, for deficiencies brought about by unsound mealtime habits or because of illness, senility, stress, or postoperative states, remember **SUR-BEX with C**. As a dietary supplement: 1 or 2 tablets daily. For postoperative convalescence: 2 or more daily.

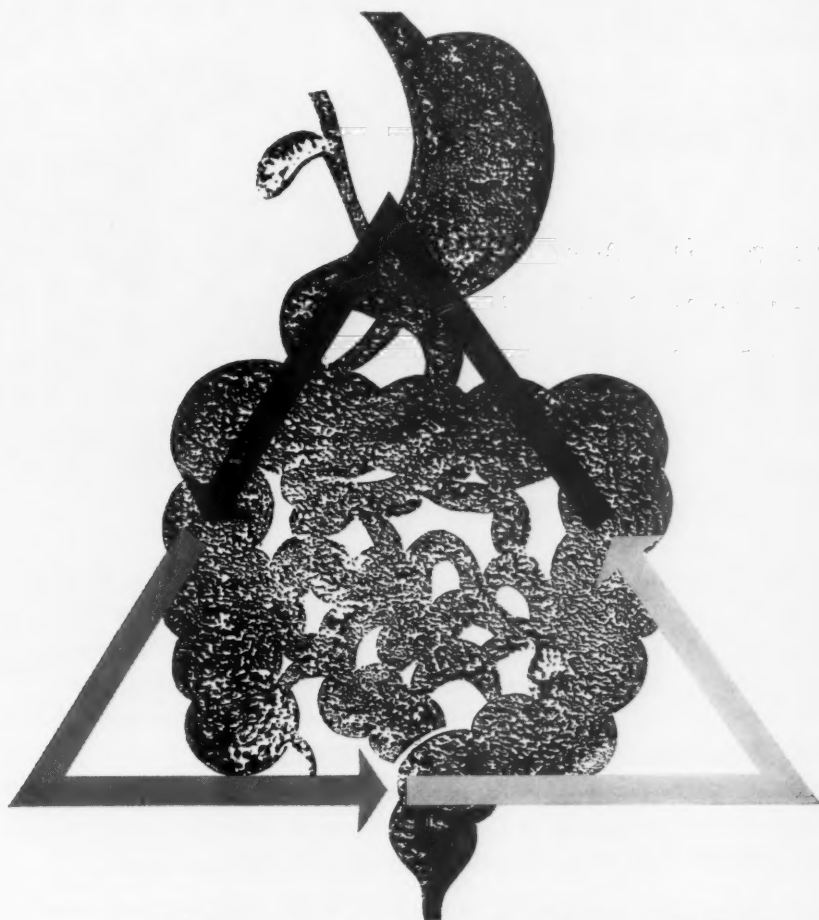
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<i>Thiamine Mononitrate</i>	6 mg.
<i>Riboflavin</i>	6 mg.
<i>Nicotinamide</i>	30 mg.
<i>Pyridoxine Hydrochloride</i>	1 mg.
<i>Vitamin B₁₂</i>	2 mcg.
(as cobalamin concentrate)	
<i>Calcium Pantothenate</i>	10 mg.
<i>Ascorbic Acid</i>	150-mg.
<i>Desiccated Liver, N.F.</i>	300 mg.
<i>Brewer's Yeast, Dried</i>	150 mg.

sur-Bex[®] with C

ABBOTT'S B-COMPLEX TABLETS WITH C



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Tridal[®]

(DACTIL[®] + PIPTAL[®]—in one tablet)

**rapid, prolonged relief throughout the G.I. tract
with unusual freedom from antispasmodic
and anticholinergic side effects**

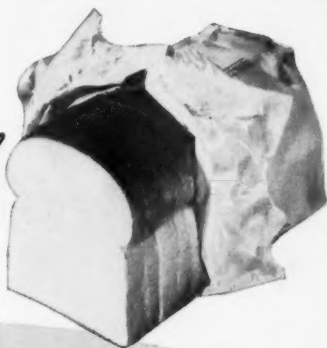
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One tablet two or three times a day and one at bedtime. Each TRIDAL tablet contains 50 mg. of Dactil, the only brand of N-ethyl-3-piperidyl diphenylacetate hydrochloride, and 5 mg. of Piptal, the only brand of N-ethyl-3-piperidyl-benzilate methobromide.

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Equally Important in
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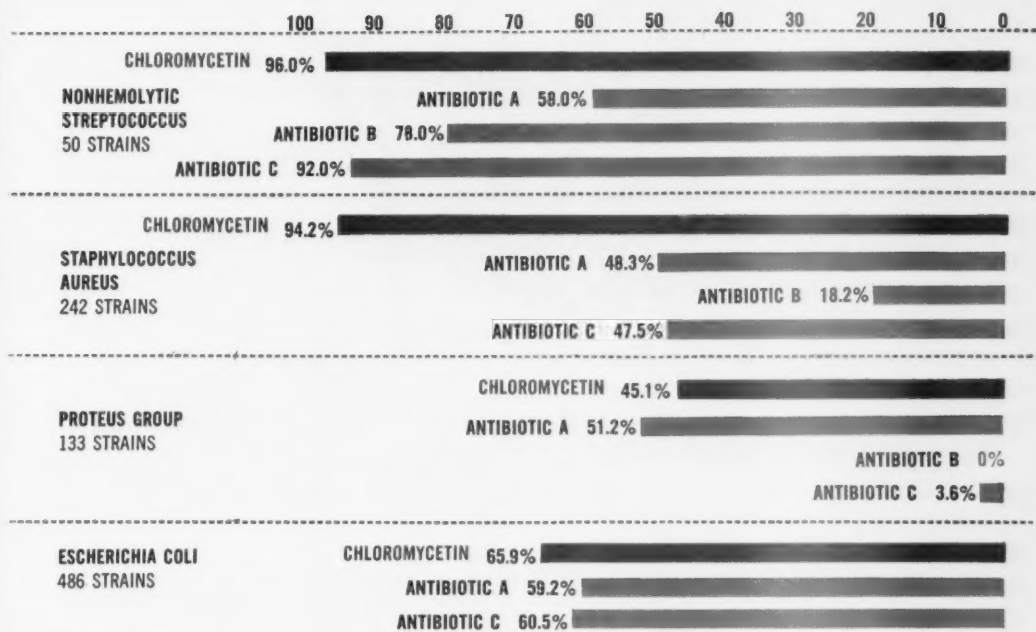
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AND TO OTHER MAJOR ANTIBIOTIC AGENTS*



*This graph is adapted from Rantz, L. A., & Rantz, H. H.: *Arch. Int. Med.* 97:694, 1956. It is based on *in vitro* studies of bacteria freshly isolated from clinical materials.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

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Now! liquid, too
 ideal for your *pediatric, geriatric, convalescent patients*

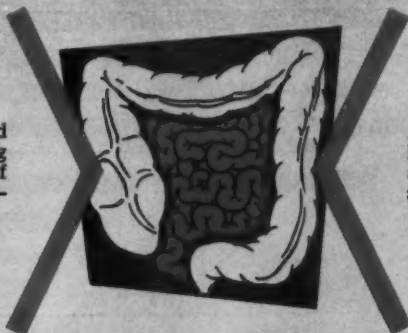


MODANE

**a nutritive
deconstipant**

**which not only relieves
but also rehabilitates**

Improves peristalsis and bowel movement, suggesting a selective stimulation of the intrinsic nerve plexus—not irritation.



Acts as a laxative on the large bowel only—does not affect motor activity of the small bowel.

Actually, a *therapeutic* approach . . . relief plus repair for the atonic bowel.

Acts surely, gently, overnight — without griping. Non-toxic, non-habit-forming.

Provides Pantothenic Acid — proven indispensable to acetyl-choline formation and normal bowel function.

Each tablet of MODANE REGULAR contains Danthron 75 mg. and Calcium Pantothenate 25 mg., Danthron to encourage peristalsis, Calcium Pantothenate for rehabilitation of the atonic bowel.

Dosage . . . MODANE REGULAR — one tablet after the evening meal. MODANE MILD (half strength, for hypersensitive, pregnant, pediatric and diet-restricted patients) — one pink tablet after the evening meal. MODANE LIQUID (one teaspoonful equals one Modane Mild tablet) — fractional or full teaspoonful, after the evening meal.

THE WARREN-TEED PRODUCTS COMPANY
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WARREN-TEED

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WITH,
OR CHANGE
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without recalculation of dosage

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oral • intramuscular • intravenous

If parenteral digitalization is imperative, or when a change in route of administration is required, DIGITALINE NATIVELLE eliminates the possible source of error associated with complex recalculation of dosage. And uncomfortable toxic symptoms occurring with dosage revision are also avoided, because DIGITALINE NATIVELLE requires only one change—to the dosage form of choice: oral, intramuscular or intravenous. All forms provide identical dosage schedules, complete absorption, equal rate of onset.

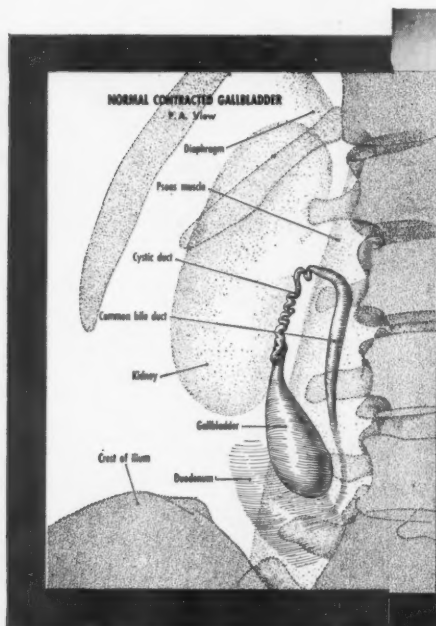
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- 1** Excellent cholecystograms are readily obtainable.
- 2** The side reactions are usually minimal, only rarely very disturbing, and often completely absent.
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Buckstein, Jacob: *The Digestive Tract in Roentgenology*. Philadelphia, J. B. Lippincott Co., 2nd ed., 1953, vol. 2, p. 1003.

Winthrop LABORATORIES

NEW YORK 18, N. Y. WINDSOR, ONT.

Telepaque (brand of Iopanoic acid), trademark reg. U. S. Pat. Off.

SUPERIOR ORAL CHOLECYSTOGRAPHY AND CHOLANGIOGRAPHY

DOSAGE:

The average adult dose of Telepaque is 3 Gm. (6 tablets). In persons of thin or medium build, weighing less than 150 lb., 2 Gm. (4 tablets) may be sufficient.

SUPPLIED:

Tablets of 0.5 Gm. in envelopes of 6 tablets, boxes of 5 and 25 envelopes, and bottles of 500.

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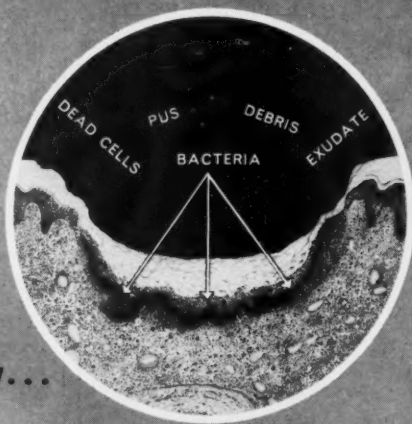
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PAGE

2	emotional disorders
3	hypertension
4	tachycardia
4	acute hypertensive crises
5	alcoholism
5	pediatric emotional problems
5	acute psychotic disturbances
6	side effects and precautions

in emotional disorders



Serpasil® provides true emotional control

In your daily practice there are undoubtedly many patients whose degree and type of emotional disturbance—characterized by overexcitation, anxiety and agitation—can *not* be adequately controlled with sedatives or weaker tranquilizers. These are the patients whom you can help most with once-a-day administration of Serpasil. For Serpasil actually sets up a “stress barrier” against anxiety and tension the patient would otherwise find intolerable. With Serpasil you can control the emotional turmoil of disturbed individuals; and because Serpasil is restricted to prescription use, control remains in your hands.

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Finnerty, F. A., Jr., and Sites, J. G.: *Am. J. M. Sc.* 229:379 (April) 1955.

in hypertension



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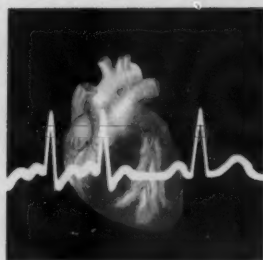
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"...a useful agent for the treatment of certain types of hypertension....The action...was increased by combining it with [Apresoline]..."²

1. Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.

2. Winsor, T.: Ann. New York Acad. Sc. 59:61 (April 30) 1954.

in tachycardia



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"Reserpine [Serpasil] was found useful in relieving the tachycardia and emotional symptoms associated with cardiac arrhythmias, thyrotoxicosis, neurocirculatory asthenia, and even coronary heart disease."

Halprin, H.: J. M. Soc. New Jersey 52:616 (Dec.) 1955.

in acute hypertensive crises



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"...the tranquilizing and anxiety-relieving properties of this drug [Serpasil] offer the possibilities of its being extremely helpful for the long-term therapy of the chronic alcoholic."

Greenfield, A. R.: *Am. Pract. & Digest Treat.* 7:241 (Feb.) 1956.

in pediatric emotional problems



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"...provided dramatic relief in remitting the syndrome of irritability in 29 of the 32 cases studied..."

Talbot, M. W., Jr.: *Ann. New York Acad. Sc.* 61:188 (April 15) 1955.

in acute psychotic disturbances



Parenteral Serpasil

The family physician is often called to subdue and arrange for quick hospitalization of patients who suddenly experience violent psychotic episodes. With intramuscular Serpasil these patients are quickly tranquilized and rendered amenable to 'quiet' hospitalization.

USUAL DOSE: 5 mg. intramuscularly followed, if necessary, by another 5-mg. intramuscular dose in 90 minutes.

"It is now possible to discreetly manage acutely disturbed psychiatric patients by the prompt administration of adequate doses of reserpine (Serpasil)."

Ayd, F. J., Jr.: *The Pharmacologic Management of Everyday Psychiatric Problems (A Scientific Exhibit).* Presented at the Clinical Meeting of the American Medical Association, Boston, Mass., Nov. 29-Dec. 2, 1955.

Serpasil:

side effects and precautions

The side effects of Serpasil are characteristic of all rauwolfia preparations.

Although millions of patients have taken Serpasil over the past several years, very few serious side reactions have been reported. There have been no cases of blood dyscrasia, liver damage, addiction or withdrawal symptoms. When patients are properly selected and the lowest effective maintenance dose is established, the physician can prescribe Serpasil confidently, with little fear of untoward reactions.

Depression

Mental depression, which has developed in a small percentage of patients treated with rauwolfia, should be differentiated from the transient change in mood or physical fatigue that is experienced by almost everyone in the general population. It should also be distinguished from the lethargy experienced by some patients on rauwolfia therapy.

In the few cases in which mental depression does occur, there is some question as to whether or not it is a direct effect of rauwolfia. According to Mayo Clinic investigators,¹ the evidence indicates that rauwolfia *per se* does not cause depression, but rather that it unmasks an underlying susceptibility to depressive reactions. Kinross-Wright² states: "It is likely that depression will occur only in a predisposed individual or in one who is already mildly depressed." Ayd,³ in a (very) recent paper, states: "That this drug may cause depression is uncertain. After reviewing a large number of so-called drug-induced depressions it appears that in some cases what was called depression was excessive tranquilization, while in the rest, the patients were depressed before the drug was started, and what the drug did was make the depression more apparent."

Whether or not it is an effect of rauwolfia, physicians and responsible members

of the patient's family should be on the alert for the development of symptoms of depression, particularly in patients with a history of pre-existing depressive tendencies. Daily doses above 0.25 mg. are contraindicated in the latter group. On withdrawal of rauwolfia, depression usually disappears, but active treatment, including hospitalization for shock therapy, has been required in some cases.

Adjunctive use of mood-elevating agents such as Ritalin is often sufficient to reverse mild depressions or drug-induced lethargy.

Other side effects

In addition to lassitude or drowsiness, other mild side effects of Serpasil include occasional nasal stuffiness and increased frequency of defecation and/or looseness of stools. Rarely, anorexia, headache, bizarre dreams, nausea and dizziness occur. With parenteral Serpasil there is a possibility of marked hypotensive effect; therefore, the blood pressure should be taken before injection and the patient kept under observation for 5 or 6 hours thereafter. Because initial doses above 0.3 mg. tend to increase gastric secretion of hydrochloric acid, daily doses above 0.25 mg. are contraindicated in patients with a history of peptic ulcer and lower doses should be used with caution.

For further details on side effects and precautions, write Medical Service Division.

1. Litin, E. M., Faucett, F. L., and Achor, R. W. P.: Proc. Staff Meet., Mayo Clin. 31:233 (April 18) 1956.
2. Kinross-Wright, V.: Wisconsin M. J. 55:1073 (Oct.) 1956.
3. Ayd, F. J., Jr.: Presented at the Sesquicentennial Convention of The Medical Society of The State of New York, New York City, Feb. 18, 1957.

SUPPLIED:

TABLETS, 0.1 mg., 0.25 mg., 1 mg., 2 mg. and 4 mg.
ELIXIRS, 0.2 mg. and 1 mg. per 4-ml. teaspoon.

PARENTERAL SOLUTION: Ampuls, 2 ml., 2.5 mg.
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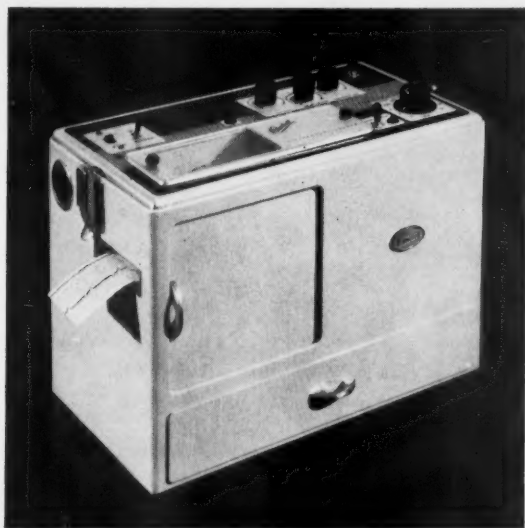
1. Johnston, R.L.: J. Indiana St. M.A. 46:869, 1953. 2. McHardy, G., and Browne, D.: Southern M. J. 45:1139, 1952.

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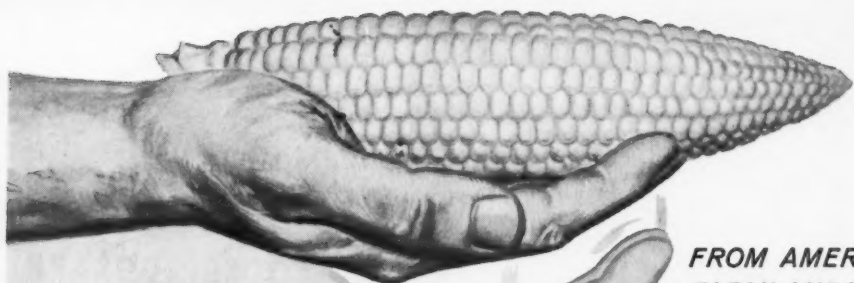
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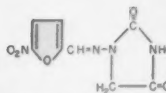
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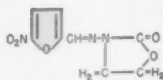
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*Dodd, M.C., and Stillman, W.S.: The in vitro bacteriostatic action of some simple furan derivatives, J. Pharm., Exp. Ther. 82: 11, 1944.

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Reference: 1. J.A.M.A. 162:1031 (Nov. 10) 1956.

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ANNALS OF INTERNAL MEDICINE

VOLUME 46

MAY, 1957

NUMBER 5

THE RELATIONSHIP OF THERAPY WITH CORTI- SONE TO THE INCIDENCE OF VASCULAR LESIONS IN RHEUMATOID ARTHRITIS *

By JAMES W. KEMPER, M.D.,† ARCHIE H. BAGGENSTOSS, M.D., and
CHARLES H. SLOCUMB, M.D., *Rochester, Minnesota*

In the last six years polyarteritis nodosa has been seen clinically, and proved histologically by biopsies, in patients who had had classic rheumatoid arthritis for many years. This association was seen only rarely prior to this time. It was our clinical impression that the administration of cortisone or corticotropin might have affected the appearance of these vascular lesions. The present study was therefore undertaken to determine the incidence and nature of peripheral vascular lesions in patients with rheumatoid arthritis, and to compare the lesions found in patients who have received adrenal cortical hormones with those in patients who have not received them.

A review of the literature concerning the vascular changes observed in patients with rheumatoid arthritis can be summarized, for the most part, as follows:

1. Perivascular or adventitial accumulations of leukocytes, plasma cells and other cells, without noticeable necrosis.¹⁻⁹
2. "Subacute" arteritis, manifested by infiltration of lymphocytes and histiocytes through all layers of the vessel wall, and possibly some exudation of fibrin and swelling of collagen, but again without severe necrosis.¹⁰⁻¹²

* Received for publication November 9, 1956.

† Abridgment of thesis submitted by Dr. Kemper to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

From the Sections of Medicine and Pathologic Anatomy, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Requests for reprints should be addressed to the Section of Publications, Mayo Clinic, Rochester, Minnesota.

3. Lesions of acute arteritis with infiltration of polymorphonuclear and other types of leukocytes and necrosis of the vessel wall, the lesions, however, being limited to one or two organs, that is, joints, heart, subcutaneous nodules, and so forth.¹²⁻¹⁵

In the last three years, however, seven reports in the literature have described the occurrence of a diffuse necrotizing arteritis with lesions similar to those of polyarteritis nodosa in patients with rheumatoid arthritis.¹⁶⁻²² Another report described a widespread arteritis with severe clinical manifestations, yet differing histologically from the usual necrotizing arteritis of polyarteritis nodosa²³; while yet another dealt with the appearance of diffuse granulomatous lesions, wherein the basic process was fibrinoid necrosis of the walls of small blood vessels.²⁴ In most of these cases, clinical manifestations of a severe, diffuse arteritis appeared during the administration or shortly after the withdrawal of therapy with cortisone or corticotropin. Because the exact relation, if any, between the administration of adrenal cortical hormones and the appearance of these vascular lesions is not clear, it was thought that a study of our own material would be enlightening.

METHODS AND MATERIALS

The histories of all patients with the diagnosis of rheumatoid arthritis that have come to necropsy at the Mayo Clinic through 1954 were reviewed. Only those cases which fulfilled the following criteria were included in this study:

1. A typical history for rheumatoid arthritis, including a polyarticular arthritis with painful swollen joints of at least six months' duration, and a progressive course for months or years.
2. Joint changes detectable on clinical examination in the form of synovial thickening and some degree of articular crippling.
3. Compatible roentgenographic changes.
4. The diagnosis of rheumatoid arthritis was made by a consultant from the section dealing with rheumatic diseases in all cases, with the exception of two cases seen prior to 1931, in which the diagnosis was made by an orthopedic consultant.
5. Those cases with septicemia and positive blood culture were excluded.
6. Cases of rheumatoid spondylitis were not included unless peripheral joint involvement was also present.
7. An adequate history of the arthritis and its progression was required.

Fifty-two cases fulfilled these requirements. The clinical histories of these patients were then studied and pertinent data were extracted. Fourteen of the patients had received cortisone and 38 had received none. The necropsy protocols and all available microscopic sections from these cases were studied in an effort to determine the presence of peripheral vascular

lesions. Hematoxylin and eosin stain was used routinely. When indicated, Verhoeff's elastic tissue stain with van Gieson's counterstain was employed. In all cases except one, routine sections taken at the time of necropsy from multiple organs were available for study. In this one exception, only sections from the heart and the liver were available. Those changes thought to be due to arteriosclerosis and those obviously due to involvement of the vessel by contiguous spread from surrounding areas of inflammation or infarction were excluded.

PATHOLOGIC ASPECTS

Evidence of vasculitis was found in 12 cases (23%). These may be divided into three groups, according to the nature of the lesions.

Group I: This consisted of five cases. The lesions were limited to the heart and consisted of thin concentric rings of collagenous fibers surrounding small arteries and arterioles. The appearance was that of "onion-skin" scars in the perivascular regions. In some vessels the muscle fibers of the media had also become involved in this process in a patchy fashion, and in other vessels the process was entirely a perivascular one.

In four of these five cases, characteristic evidence of rheumatic heart disease was present in the form of other pathologic lesions, including myocardial Aschoff bodies and rheumatic valvular disease. The vascular lesions described as being found in this group have been found by others in patients with rheumatic fever, and the vascular changes in these patients were probably related to rheumatic fever. None of the patients in group I had received cortisone or corticotropin. The patients in this group will not be considered further.

Group II: This consisted of three cases. The lesions in this group were considered to be an active, acute vasculitis, with infiltration of polymorphonuclear leukocytes and fibrinoid degeneration involving all layers of the vessel wall, but were limited to one organ, and in two of the cases, to one vessel. Lesions similar to those in group I were also present. None of the patients in group II had received cortisone or corticotropin. The lesions in group II were considered to be nonspecific and will not be considered further.

Group III: The most interesting and undoubtedly the most significant lesions were found in the four cases comprising group III. These lesions were similar to those of classic polyarteritis nodosa. All four of these patients had received cortisone therapy. Most frequently the vessels involved were medium-sized and small arteries and arterioles, but larger arteries and even venules, veins and capillaries were involved occasionally. In three of the four cases, lesions were widespread, involving almost all organs, including heart, liver, spleen, pancreas, adrenals, kidneys, gastrointestinal tract, gall-bladder, lymph nodes, skeletal muscle, skin, synovia and peripheral nerves. The absence of pulmonary lesions in these three cases

was striking. In the fourth case, lesions were less widespread and will be described later.

In the first three cases, lesions were seen in various stages: In the acute stage, there was necrosis with cellular exudation and partial or total destruction of one or more layers of the vessel wall (figure 1). In some lesions the exudate consisted primarily of polymorphonuclear leukocytes, but the most frequently encountered exudate was one which contained lymphocytes, plasma cells and other mononuclear cells. Occasionally, large numbers of eosinophils were noted.

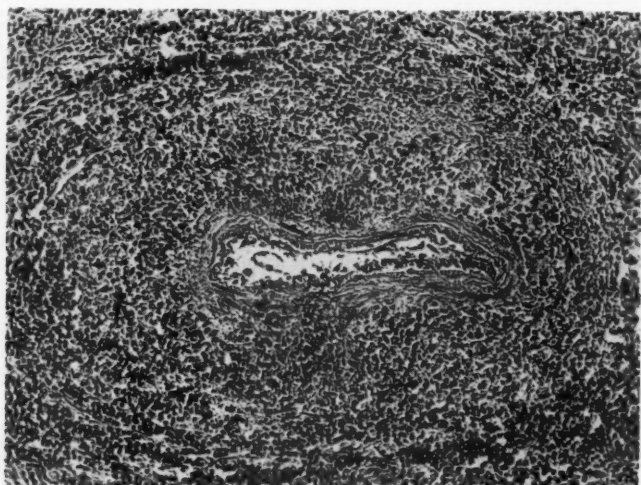


FIG. 1. Case 2. Arteriole in a section of liver. Acute necrotizing arteritis. The vessel wall has been destroyed by necrosis and a polymorphonuclear cellular exudate extends to the inner media. Fibrinoid necrosis has destroyed the intima (hematoxylin and eosin; $\times 140$).

In other vessels the lesions appeared to be in a subacute stage. There was a broad band of fibrinoid necrosis involving the intima and subjacent media, with the formation of granulation tissue in the outer media and adventitia (figures 2 and 3). This was the type of lesion encountered most frequently. This granulation tissue was made up of proliferating fibroblasts and capillaries and of lymphocytes and other mononuclear cells. The internal elastic membrane was usually seen to be disrupted and fragmented. Infrequently, the band of fibrinoid necrosis involved primarily the media, the granulation tissue being seen on either side of this layer. Intimal proliferation was frequently conspicuous. In no cases were lesions seen that were completely healed. Thrombosis and aneurysm formation were encountered only rarely.

Occasionally, lesions were seen which bore a resemblance to some of

the histologic features of the rheumatoid subcutaneous nodule (figures 4 and 5). In the region of the intima there were proliferating endothelial cells, plasma cells and lymphocytes, together with unidentified mononuclear

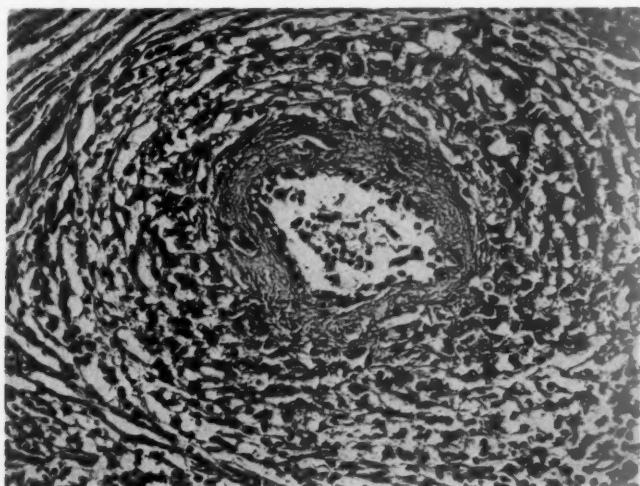


FIG. 2. Case 2. Arteriole from the adrenal capsule. Subacute arteritis. A broad band of fibrinoid necrosis involves and replaces the intima and subjacent media. An edematous granulation tissue with proliferating fibroblasts and capillaries involves the media and adventitia. There is an infiltration of lymphocytes and other mononuclear cells (hematoxylin and eosin; $\times 245$).

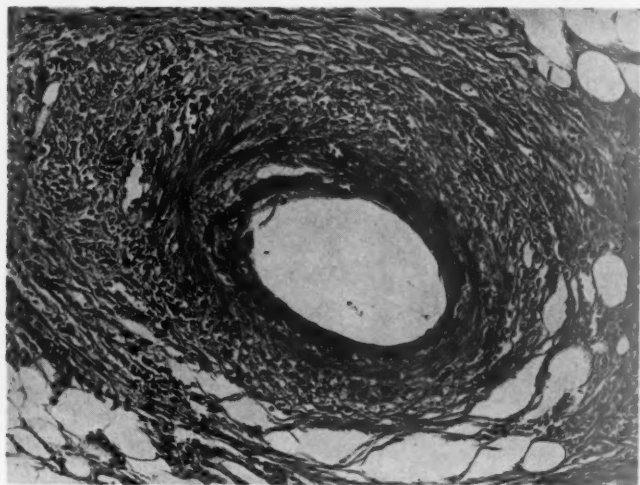


FIG. 3. Case 3. Small artery from a section of sciatic nerve. Fibrinoid necrosis has destroyed the intima. In the surrounding layers there is necrosis with a mild cellular reaction (hematoxylin and eosin; $\times 150$).

cells. Surrounding this was a band of amorphous or "fibrinoid" necrosis with nuclear debris. External to this, in the region of the adventitia, was the palisading of radially arranged fibroblasts with elongated nuclei fre-

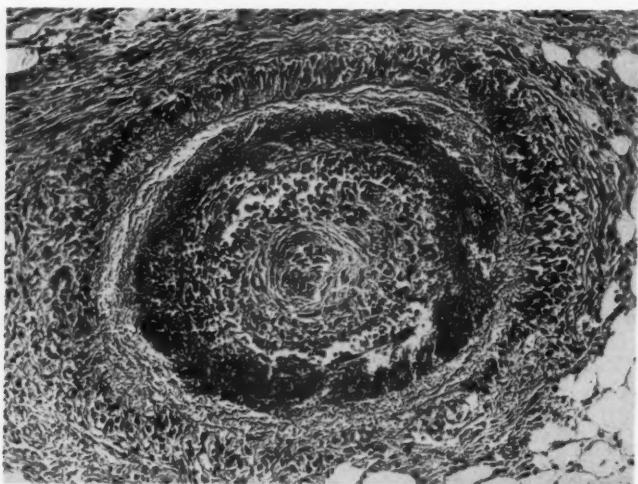


FIG. 4. *Case 2.* Arteriole from a section of sciatic nerve. There is intimal proliferation, and the media is replaced by necrosis and cellular reaction. In the outer media there is a band of fibrinoid necrosis surrounded by radially arranged fibroblasts in palisade formation (hematoxylin and eosin; $\times 130$).

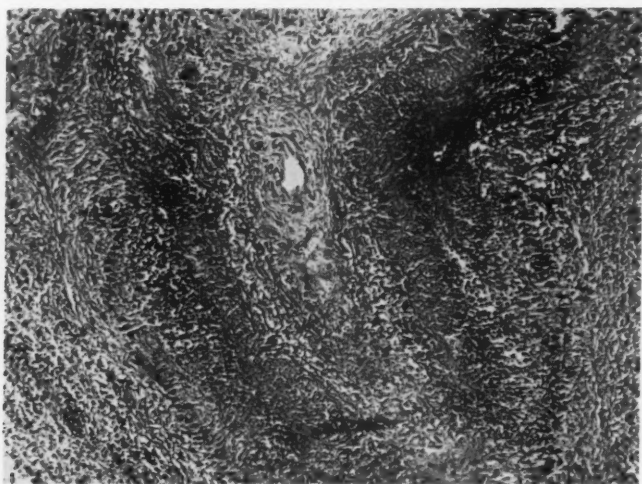


FIG. 5. *Case 3.* Arteriole from the spleen. There is almost complete destruction of normal architecture of the vessel wall. Note the three distinct zones: an inner zone of intimal proliferation, a middle zone of fibrinoid necrosis and scattered necrotic cellular debris, and an outer zone of radially arranged fibroblasts in palisade formation. Two giant cells are present (hematoxylin and eosin; $\times 100$).

quently seen in subcutaneous nodules. Occasionally, giant cells could be seen. This type of lesion was seen in all three of these cases. None of these three patients had subcutaneous nodules. In one case, extravascular granulomatous lesions, with a structure histologically similar to that of the rheumatoid nodule, were noted in the heart. These were similar to those described by others²⁵ and were not investigated in detail in the present study.

In the last case in this group (case 4), lesions were limited to the kidneys, adrenal glands, ascending colon and right sciatic nerve. The lesions were also those of a subacute arteritis, but consisted mostly of mononuclear and lymphocytic cellular infiltration, edema and fibroblastic proliferation (figure 6). Necrosis was not so extensive as in the other three cases.

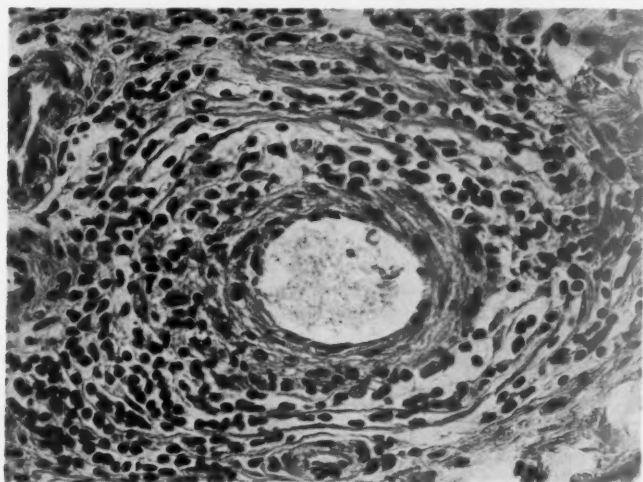


FIG. 6. Case 4. Arteriole from the renal capsule. Subacute arteritis. A predominantly mononuclear and lymphocytic cellular infiltration involves all layers of the vessel wall. Necrosis is minimal (hematoxylin and eosin; $\times 380$).

Because of the importance of the vascular lesions in the four cases in group III, the clinical histories and necropsy findings in these four patients will now be described in detail.

CASE REPORTS

Case 1. A 56 year old white man was first seen at the clinic in September, 1950. In 1945 he had begun to have recurrent episodes of polyarthritis, with red, swollen, tender joints. The diagnosis of rheumatoid arthritis had been made and he had been given gold therapy for 20 weeks. In August, 1950, his family physician had begun administration of cortisone: 100 mg. daily for four days, then 25 mg. daily thereafter. The response was good, with control of his joint stiffness and pain. On the twenty-third day of cortisone administration a recurrent sore throat had developed. Seven days later tonsillectomy had been done, and both tonsils had

been found to be grossly infected. Thirty-six hours after operation a rise of temperature had suddenly developed and marked hemorrhagic changes had appeared in the skin of both lower extremities. Cortisone had been discontinued on this day. The blood pressure had dropped from a prior level of 138/80 mm. of mercury to 90/60. Bloody diarrhea had suddenly ensued, and in the next 24 hours the patient had passed 11 bloody stools. Treatment for peripheral vascular collapse had been instituted, and the patient had been given digitalis and antibiotic therapy. Within 24 hours he felt well. Blood pressure had returned to normal, and the bloody diarrhea had stopped.

Four days after cessation of cortisone therapy, administration of corticotropin, 20 mg. every six hours, had been begun in an effort to control joint symptoms. Five days subsequent to this, postpharyngeal edema without stridor had developed. Administration of corticotropin had been abruptly stopped, and treatment with diphenhydramine hydrochloride (Benadryl) and epinephrine had been started. In 20 minutes symptoms had completely subsided. Two similar episodes had occurred in the next 48 hours. On September 13, two weeks after the first episode of bloody stools, another episode of bloody diarrhea had occurred. The skin lesions were still present, and some had become necrotic. The patient was then referred to the clinic.

On admission to the clinic, on September 14, 1950, the patient appeared acutely ill and dehydrated. Blood pressure was 100 mm. of mercury systolic and 60 diastolic, pulse rate, 110 beats per minute, and temperature was normal. He had not received corticotropin for nine days or cortisone for 18 days. Hemorrhagic skin lesions were present over the trunk, hands, face and legs. Over the anterior tibial surfaces, several of these lesions had become necrotic. Examination of the lungs, heart and abdomen was negative. Many of the joints were stiff, and residual damage to the left wrist was apparent. Active synovitis, however, was absent. Deep tendon reflexes in the arms and legs were absent. Pain sensation in the extremities was diminished. In addition to the previous history, it was learned that the patient had noted weakness of his left hand for three weeks and weakness of his right hand and both feet for one week. His feet had been "numb" for one month.

Significant laboratory data were as follows: hemoglobin and erythrocyte count, normal; leukocytes, 29,000 cells per cubic millimeter of blood, with a differential count of 10 lymphocytes, three monocytes, 86 neutrophils and one eosinophil; erythrocyte sedimentation rate, 83 mm. in one hour (Westergren method); two blood cultures, negative. Roentgenograms of the left wrist were interpreted as showing old rheumatoid arthritis with destructive changes.

Treatment was started with cortisone, penicillin and intravenous fluids. The patient first appeared slightly improved, but in the next two days his condition became progressively worse. His oral temperature remained around 100° F. On the fourth day after admission he went into circulatory collapse and died. He had received 1,100 mg. of cortisone over a period of 32 days prior to onset of symptoms related to his terminal illness. The total dose of steroid hormones was 1,600 mg. of cortisone and 400 mg. of corticotropin.

Necropsy was performed four hours after death. Significant findings included 1 L. of clear fluid in the left pleural cavity, several small pulmonary infarcts, two small saddle emboli at a bifurcation of the pulmonary artery, and a grayish yellow area of myocardial softening measuring 3 by 2 cm. in the posterior portion of the septum. Throughout the jejunum, ileum, cecum, sigmoid and rectum were numerous hemorrhagic ulcerations of the mucosa measuring 1 to 2 cm. in diameter.

Histologic examination revealed the vascular lesions already described in the heart, lymph nodes, liver, pancreas, spleen, gastrointestinal tract, adrenals, kidneys, prostate, skin, synovia, skeletal muscles and diaphragm. Sections of peripheral

nerves also revealed these lesions in the right sciatic nerve, left brachial plexus, celiac ganglion and right lumbar plexus. In sections of the gastrointestinal tract it was possible to demonstrate acute angitis in vessels adjacent to, but not directly involved by, areas of mucosal infarction. It therefore seems reasonable that many of the ulcers seen were secondary to the vascular lesions.

The following anatomic diagnoses were made: (1) polyarteritis nodosa with multiple infarcts of kidneys, heart, lungs, adrenals and skin; (2) multiple ulcers of ileum and colon with gastrointestinal hemorrhage; (3) multiple pulmonary emboli; (4) atrophy of cortex of adrenals with absence of lipoid.

Case 2. A 48 year old white woman was first seen at the clinic on June 26, 1951. Since 1947 she had experienced repeated episodes of painful swelling involving her feet, ankles, knees, hands, wrists and elbows, with much stiffness and progressive crippling.

In February, 1951, she had consulted a local internist, who made a diagnosis of rheumatoid arthritis and began corticotropin therapy. From March 25 to April 25 she had received 40 mg. daily and had noticed marked improvement in her joint symptoms and exercise tolerance. She had had difficulty in sleeping, had developed a ravenous appetite, had become extremely nervous and restless and had wanted to "keep on the go." She had noted cramping epigastric pains, relieved by food. At this time, cortisone had been substituted for corticotropin. She had received 100 mg. daily in four divided doses orally. She had maintained her previous improvement in the arthritic manifestations, but an increased growth of facial hair and increased severity of the cramping epigastric pain had developed.

On May 15, 1951, after three weeks of cortisone therapy (seven weeks after initiation of corticotropin therapy), she had begun to notice "numbness and tingling" of the dorsa of both feet, associated with diminished sensation of "feeling" in these areas. The dose of cortisone had been increased to 150 mg. daily for three days, without benefit. The dosage had then been decreased to 100 mg. daily. On May 30, 1951, a severe, sharp pain in the arch of the left foot developed, with accompanying pain extending along the medial aspect of the left thigh and along the distribution of the left sciatic nerve. On June 2, 1951, she had found that she could not dorsiflex her left foot. She had been hospitalized elsewhere and the dose of cortisone had been reduced to 75 mg. daily.

On June 26, 1951, the patient was referred to the clinic. She stated that the paresthesias and pains in the left lower extremity were decreasing and bothered her only on weight-bearing, although she still had a left drop foot. Her only joint pain at that time was in the feet on walking. She appeared stimulated and jittery, and apparently had much nervous energy beyond her physical resources. She related that she slept irregularly, ate more than usual, and in the last two weeks had noted puffiness of her cheeks and roughening of her skin. She exhibited emotional lability, with frequent crying, restlessness, and anxiety amounting almost to panic at times. She stated that when she went too long without a dose of cortisone she would feel "sick," weak, restless and disturbed; but immediately after a dose of cortisone she would feel relieved, provided food was taken with it. If no food was ingested with the dose, epigastric cramping would develop within one hour.

Examination revealed a thin, pale, tired-looking white woman. Blood pressure, pulse and temperature were normal. Her face appeared rounded, and there were numerous small, acnelike lesions of the skin. Examination of the joints revealed swelling and limitation of movement of the joints of the hands, elbows, knees and ankles, and tenderness on palpation of the temporomandibular joints, fingers, knees and ankles. The fingers showed ulnar deviation. Neurologic examination revealed a left drop foot, bilateral weakness of the dorsiflexors of the wrist and diminished vibratory sensation over both ankles and feet. It was felt that she presented many features consistent with chronic hypercortisonism.

Pertinent laboratory findings were as follows: hemoglobin and erythrocyte count, normal; leukocytes, 9,500 cells per cubic millimeter of blood, with a differential count of 10 lymphocytes, one monocyte, 88 polymorphonuclears and one eosinophil; erythrocyte sedimentation rate, 100 mm. in one hour (Westergren method). Roentgenograms of the joints were interpreted as showing rheumatoid arthritis, with destructive changes involving both wrists, phalanges, metacarpophalangeal joints, and the joints of both feet.

The dose of cortisone was reduced to 50 mg. daily. A toxic organic psychosis developed, requiring the patient's transfer to a closed psychiatric ward for several days. On July 4 the dose of cortisone was reduced to 37.5 mg. daily. The next day the neurologic examination was repeated and revealed a loss of function of the flexors and extensors of the right ankle, in addition to the loss of function of the flexors of the left ankle present on the initial examination. Both ankle jerks were absent and the peripheral sensory changes were the same as previously. By July 12 there were symptoms and signs of a left median nerve palsy. A spinal puncture revealed normal findings. The patient failed to show improvement and steadily became weaker. Hemograms remained essentially unchanged. The neurologic picture became more that of a diffuse peripheral neuritis than of a mononeuritis multiplex.

On the morning of August 12 the patient was found to be unresponsive and unable to talk. There was a right lower facial weakness. The impression was that she had suffered a cerebrovascular accident. She remained in coma, Cheyne-Stokes respirations developed and she died the same day. She had received 2,100 mg. of cortisone and 1,200 mg. of corticotropin over a period of seven weeks prior to the onset of her terminal illness. The total amount of hormones administered was 1,200 mg. of corticotropin and 7,500 mg. of cortisone.

Necropsy was performed 16 hours after death. Significant findings were as follows: Each pleural cavity contained 300 c.c. and the peritoneal cavity contained 500 c.c. of clear yellow fluid. There was a shaggy, fibrinous exudate on both the visceral and parietal pericardium. On the surface of the liver were numerous dark bluish areas measuring 3 by 2 cm. On cut sections these dark areas were seen throughout the liver. In the center of each area was a yellowish white nodule with a punctate opening in the center, which appeared to be a thickened blood vessel.

The stomach contained 500 c.c. of dark red blood. In the stomach, small intestine, large intestine and rectum could be seen numerous tiny, thickened blood vessels, especially in the submucosa. These blood vessels were thickened for a considerable length in some areas, and in other areas the thickening was focal. The thickened blood vessels were tortuous, and on cut section had a pinpoint lumen. The pancreas appeared grossly normal, but on cut section similar thickened blood vessels with pinpoint lumina could be seen. Small white nodules containing a tiny reddish dot in the center were seen in cut sections of the kidneys and urinary bladder. These apparently represented thickened blood vessels with a pinpoint lumen.

Examination of the brain revealed a moderate amount of subarachnoid hemorrhage over the left base. Sectioning revealed a massive intracerebral hemorrhage on the left side, with extension of the hemorrhage into the ventricles. The destruction of brain tissue on the left was great, extending from the midfrontal to the occipitoparietal junction. The basal ganglia and thalamus on the left were destroyed, and the destruction had extended in the distribution of the anterior and middle cerebral arteries. The ventricles were filled with blood. No sclerosis and no aneurysms were noted.

Histologic examination revealed the previously described vascular lesions in the heart, liver, pancreas, spleen, gastrointestinal tract, adrenals, kidneys, diaphragm, skeletal muscle, lymph nodes and synovia, and in sections of the following peripheral

nerves: radial, ulnar, median, peroneal and sciatic. No inflammatory vascular lesions could be demonstrated in the brain.

The following anatomic diagnoses were made: (1) polyarteritis nodosa; (2) cerebral hemorrhage (left basal nuclei with rupture into the ventricles); (3) infarcts of liver and spleen; (4) fibrinous and fibrous pericarditis.

Case 3. A 63 year old white woman was first seen at the clinic on May 2, 1954. Her arthritis had had its onset in 1936, with pain and swelling in the knees and ankles. Following this, her shoulders and hands had become involved in the arthritic process, and progressive crippling had ensued during the next 15 years in spite of alternate partial remissions and exacerbations. She believed that she had received five or six gold injections previously, but was not sure of the date.

In 1952 she had begun to have an increase in the severity of her symptoms, with painful swelling of her feet and ankles, stiffness after inactivity, and severe pain in her legs, shoulders and neck. In May, 1952, her local physician had begun the administration of cortisone. She had received 40 mg. a day orally for two months, and had taken 30 mg. daily thereafter. She had experienced no relief in her symptoms as far as she could recall. Approximately three months later she had noted puffiness of her face and increased growth of facial hair. Her arthritis had gone on to progressive crippling until by February, 1954, she was hardly able to get out of bed. She had then been hospitalized near her home because of increased pain in her legs and feet. She noted numbness and tingling, and a "dead feeling" in her right foot. The cortisone was switched to hydrocortisone, 30 mg. a day orally, but no relief of symptoms occurred. Severe pain over the lateral aspect of her right hip developed, which seemed to extend down to her right foot. She also had pain in her left leg, and the soles of her feet and toes were "numb" and painful on weight-bearing.

For the last month she had experienced auditory and visual hallucinations, according to the description given by the nurse who accompanied the patient to Rochester. For the last week she had also complained of tingling in her hands. For two months she had noted anorexia.

Physical examination at the time of admission revealed a bedridden, chronically ill, confused white woman. There were multiple joint deformities typical of residual rheumatoid arthritis. Blood pressure was 150 mm. of mercury systolic and 90 diastolic, the pulse rate was 120 beats per minute and the oral temperature was 99.2° F. There was moderate hirsutism of the cheeks and upper lip, and her face was rounded. Examination of the chest revealed dullness to percussion and moist râles in the base of the left lung. Examination of the joints showed residual rheumatoid deformity in the elbows, wrists and hands, with subluxation of the metacarpophalangeal joints and hyperextension of the proximal interphalangeal joints. There were swelling and tenderness also of the knees and ankles. Light touch sensation was diminished over the left foot, and the right knee jerk was diminished. Both ankle jerks were absent. It was felt that many features of chronic hypercortisonism were present.

Pertinent laboratory data were as follows: hemoglobin, 9.2 gm. per 100 c.c. of blood; erythrocytes, 3,160,000 cells per cubic millimeter of blood; leukocytes, 14,100 cells per cubic millimeter of blood, with a differential count of nine lymphocytes, one monocyte, 88 polymorphonuclears and two eosinophils; erythrocyte sedimentation rate, 120 mm. in one hour (Westergren method); L.E. clot reaction, negative; two blood cultures, negative. Roentgenograms of joints were interpreted as showing destructive changes involving most joints of the right foot, and old destructive changes in the right ankle joint consistent with rheumatoid arthritis.

Hydrocortisone was continued in a daily dose of 30 mg. orally, and sedation was given. On May 5, 1954, the dose of hydrocortisone was increased to 40 mg. a day, orally. On May 5 the patient was noted to have slurred speech and a right facial

droop. She seemed well oriented. Neurologic examination revealed right facial weakness, left hemiparesis and weakness of the right upper extremity. Vibratory sensation over the lower extremities was diminished. The neurologic consultant made a diagnosis of cerebral infarction.

The neurologic symptoms and signs progressed. By the next day there were left hemiplegia and almost complete loss of function of muscles supplied by the right radial nerve, with partial involvement of the right median and ulnar nerves. On May 7, 1954, the dose of hydrocortisone was increased to 50 mg. a day, orally. The patient's course was steadily progressive and, in spite of supportive treatment and intravenously administered hydrocortisone, she died quietly on May 13, 1954. She had received 19.5 gm. of cortisone over a period of 21 months prior to onset of her terminal illness. The total amount of cortisone given was 22.65 gm.

Necropsy was performed five hours after death. The right pleural cavity contained 1,000 c.c. of clear straw-colored fluid. The heart weighed 360 gm. A fibrinous exudate covered the epicardium. The lungs appeared congested and edematous, with a meaty consistency. On cut surface one could see firm gray granular areas up to 2 cm. in diameter scattered throughout both lungs.

The vessels over the surface of the gall-bladder were prominent, white and nodular. There was a chronic ulcer on the lesser curvature of the stomach in the prepyloric area measuring 2 by 2.5 cm. The stomach contained a moderate amount of bloody mucus, as did the duodenum, jejunum and upper ileum. The serosa over the head of the pancreas contained vessels similar to those described in the gall-bladder. The adrenals appeared pale and the cortices atrophic. The surface of the kidneys was finely granular. The synovial membrane from the right knee was hypertrophied and covered with fronds measuring up to 2 cm. in length. The cartilage was firm, rough and granular.

Examination of the brain revealed no abnormalities except for the basilar artery. In the midportion of this vessel was a symmetric fusiform thickening of the vessel wall. In this region, measuring 6 mm. in length, the wall of the vessel was 2 mm. in thickness in all portions, and the lumen was narrowed to an extremely small size. There was an area of softening in the right side of the pons measuring 1 cm. in diameter.

Histologic examination revealed necrotizing arteritis in the heart, spleen, gastrointestinal tract, pancreas, gall-bladder, liver, kidneys, adrenals, thyroid, diaphragm, skeletal muscle, basilar artery, brachial plexus, right sciatic nerve and choroid plexus. Although several thick-walled vessels were present in the base of the gastric ulcer, no active arteritis could be demonstrated. It is thus impossible to say with certainty whether the vascular lesions were important in the pathogenesis of the ulcer, even though acute arteritis was present in other portions of the gastrointestinal tract.

The following anatomic diagnoses were made: (1) polyarteritis nodosa (generalized); (2) thrombus in basilar artery with infarct of the right pons; (3) bilateral pulmonary edema; (4) recent and organizing bilateral bronchopneumonia; (5) healing infarcts of the lateral wall of the left ventricle; (6) fibrous and fibrinous pericarditis; (7) granular kidneys with old infarcts; (8) chronic ulcer of the stomach with hemorrhage; (9) atrophy of the adrenal cortices.

Case 4. A 51 year old white man had first been seen at the clinic in 1933 at the age of 30 years. Two months previously he had experienced an episode of swelling, pain and redness in his knees, and soon the process had spread to involve his ankles, elbows, wrists, fingers and feet. A diagnosis of rheumatoid arthritis had been made, and over the next two years progressive joint involvement with deformity had occurred.

The patient was not seen again until November, 1950, at the age of 47 years. He again described a progressive polyarthritis that had involved most of his peripheral

joints. Examination revealed mild bilateral conjunctivitis. The spleen was enlarged to 2 cm. below the left costal margin. The wrists, elbows, knees, ankles and shoulders were tender, swollen and limited in motion. Ulnar deviation of the fingers and hammer toes were present. Laboratory studies showed a normal erythrocyte count and hemoglobin, with a leukocyte count of 4,300 cells per cubic millimeter of blood. The erythrocyte sedimentation rate was 87 mm. in one hour (Westergren method). Roentgenograms again revealed destructive changes in the left wrist and knee.

Because of the progressive course, cortisone therapy was begun in December, 1950. The initial dose was 100 mg. daily, and the dose was gradually reduced. After 10 days of therapy the patient estimated that he had experienced 50% relief of his symptoms, and the sedimentation rate had fallen from 96 mm. in one hour to 58 mm. in one hour (Westergren method). Gradual reduction was continued, with progressive improvement until a dose of 37.5 mg. per day was reached, at which time a flare of the arthritis appeared. The patient was then maintained on a dose of approximately 62.5 mg. daily, with supplemental doses of aspirin for the next few months. No signs of hypercortisonism were noted. After a bout of influenza it became obvious that the arthritis was not under control, and the patient felt that he had lost all of the benefit from hormone therapy. The dose was gradually reduced and administration was discontinued on May 25, 1951. Over a period of 175 days of hormone therapy a total dose of 10.14 gm. of cortisone had been given. During withdrawal, severe weakness, increased articular pain and aching, fatigue, muscular stiffness and depression developed. The patient was dismissed with a view toward considering another course of cortisone therapy at a later date.

Unfortunately, the patient was never examined again at the clinic, and no further record is available until the time of his death in August, 1954. It was learned that he had been taking cortisone in large doses for a considerable period prior to his death. The dosage, or the presence or absence of symptoms of hypercortisonism, is not known.

Necropsy was performed 11 hours after death. The only significant gross findings were a localized necrotic purulent area in the pleura on the right side, 5 cm. in diameter, and some superficial ulcers on the mucosal surface of the colon.

Histologic examination revealed lesions of acute arteritis, without marked necrosis, in the kidneys, adrenals, colon and right sciatic nerve. As in case 1, the proximity of acute vascular lesions to the infarcts and ulcers in the colon seemed to indicate that the former may have been an important factor in causing the latter.

The following anatomic diagnoses were made: (1) necrotizing arteritis (adrenals, kidneys, colon, sciatic nerve); (2) atrophy of the cortices of the adrenal glands; (3) multiple infarcts with confluent pseudomembranous ulcers of the colon; (4) focal suppurative encapsulated pleuritis of the right middle lobe; (5) chronic rheumatic mitral endocarditis.

The pertinent data regarding these four patients are summarized in table 1.

COMMENT

In this study the answers to two questions were sought: First, what are the incidence and nature of peripheral vascular lesions in rheumatoid arthritis at necropsy? Second, what is the relation between these lesions and therapy with adrenal cortical hormones?

As was previously stated, the over-all incidence of vasculitis in this series was 23%, but the incidence of widespread, necrotizing arteritis was

TABLE 1
Summary of Clinical Data on Four Patients with Disseminated Necrotizing Arteritis

Data	Case Number			
	1	2	3	4
Age, years	56	48	63	51
Sex	Male	Female	Female	Male
Clinical signs of arteritis	Yes	Yes	Yes	Unknown*
Duration of arthritis, years	5	4½	18	21
Gold therapy	Yes	No	?	No
Corticotropin therapy	Yes	Yes	No	No
Cortisone therapy	Yes	Yes	Yes	Yes
"Hypercortisonism"	No	Yes	Yes	Unknown*
Duration of hormone therapy prior to signs of arteritis	32 days	7 wks.	21 mos.	Unknown*
Average daily dose of cortisone, mg.	33	100	30.9	Unknown*
Total cortisone prior to clinical onset of arteritis, gm.	1.1	2.1	19.5	Unknown*
Total corticotropin prior to arteritis, gm.	0	1.2	0	0
Duration of life after onset of clinical symptoms of arteritis	3 wks.	3 mos.	3 mos.	Unknown*

* No clinical data were available on this patient for three years prior to his death. It was known that he had been receiving "large" doses of cortisone up to the time of death.

8%. It is difficult to find any accurate estimates of the expected incidence of disseminated necrotizing arteritis in routine necropsies. Boyd²⁶ found that the incidence of polyarteritis nodosa varied from two in 1,600 to 12 in 17,000 necropsies. Rich²⁷ found six cases of polyarteritis nodosa in 10,036 routine necropsies at the Johns Hopkins Hospital between 1916 and 1935, and 32 cases in 4,483 necropsies between 1936 and 1944. He ascribed the difference to the introduction of sulfonamide drugs. At any rate, it would appear that the incidence of this type of arteritis in the present series of patients with rheumatoid arthritis is considerably greater than one might expect in a group of routine, unselected necropsies. The possibility that this is a chance, coincidental association of the two diseases seems unlikely. The next consideration is, To what can this finding be attributed and what is the relation between these lesions and the administration of adrenal cortical hormones?

Fourteen of the patients (27%) had received adrenal cortical hormones. Four of these showed evidence of chronic hypercortisonism. All four patients with necrotizing arteritis had received adrenal cortical hormones, and at least two of these showed features of chronic hypercortisonism. Unfortunately, the status of case 4 in this regard could not be determined. In addition to the usual features associated with Cushing's syndrome, one of us has described a syndrome consisting of the triad of cyclic mood changes, fatigability, and muscle and joint aching occurring in patients with rheumatoid arthritis given large doses of adrenal cortical hormones for prolonged periods.^{28, 29} Two of the four patients with chronic hypercortisonism

demonstrated these features, in addition to the more obvious features associated with Cushing's syndrome.

Careful analysis of the clinical records was done to compare the four patients who had disseminated necrotizing arteritis with the remainder of the patients in this series. No significant difference between the two groups could be found in regard to the onset, manifestations, severity or progression of the arthritis, or to the treatment received, except for the administration of cortisone and evidences of hypercortisonism in the group with arteritis.

Ten of the patients without necrotizing arteritis (21%) and one of the patients in the group with arteritis (25%) had hypertension. A history of allergy was obtained in seven (15%) of the group not showing arteritis and in two (50%) of the patients with arteritis. This would indicate a somewhat higher incidence of allergy in the latter group; however, the numbers are too small for valid conclusions. Five of the patients not having arteritis (10%) had received gold therapy, while only one (25%) of the four patients with arteritis had received gold. This was discontinued for a considerable period before the onset of symptoms attributed to arteritis. Practically all of the patients in both groups had received salicylates, and there was nothing to indicate that the patients with necrotizing arteritis had received any larger amounts than the rest of the patients.

It is interesting, however, that all four of these patients with widespread necrotizing arteritis had received cortisone and that at least two of these were in the "hypercortisone" group. It is true that the number of cases is small, but nevertheless an explanation is required for the fact that in four (29%) of 14 patients receiving cortisone therapy for rheumatoid arthritis, widespread necrotizing arteritis developed, while in none of 38 similar patients receiving no therapy with adrenocortical hormones did these lesions develop.

It is probable that patients receiving favorable results from cortisone therapy for rheumatoid arthritis and dying of some other cause would be less likely to die in a hospital and be included in a necropsy series than patients having a course similar to that of these four patients. Mainland³⁰ and Berkson³¹ have shown how false conclusions can be obtained from relying on necropsy and hospital data in determining the incidence of diseases. In a necropsy study of this kind, patients with the more severe and bizarre ailments are more likely to be included. However, this would apply to patients seen in the precortisone era as well, and this factor, by itself, could not account for the differences found between the group receiving cortisone and the group not receiving cortisone.

There have been very few reports in the literature wherein lesions of a widespread necrotizing arteritis have been demonstrated in well documented cases of rheumatoid arthritis in which the patients had not received cortisone or corticotropin. Furthermore, most of these have been isolated cases, or cases in small select groups, and their significance in the over-all picture is hard to evaluate.

The clinical manifestations of so-called "panmesenchymal reactions" occurring in patients with rheumatoid arthritis during cortisone therapy have been well documented. In 1952 one of us (Slocumb²⁸) described the clinical experience at the Mayo Clinic with patients manifesting the syndrome of chronic hypercortisonism. This syndrome is induced by the exogenous administration of cortisone or corticotropin. In addition to the obvious signs associated with Cushing's syndrome there are more subtle changes, including cyclic changes of mood ranging from a feeling of restless drive to one of exhaustion, marked fatigability, and aching muscles and joints. The latter rheumatic manifestations may be confused by both the patient and his physician with a flare of the rheumatoid arthritis.

A later report²⁹ described the clinical picture occurring on withdrawal of cortisone therapy in these patients. Abrupt withdrawal may produce the clinical picture of acute hypoadrenia and profound symptoms of a "panmesenchymal reaction." Gradual reduction of the dose of cortisone may cause a "panmesenchymal reaction," which may be mild and transient or severe and prolonged. These reactions simulate a rheumatoid flare, lupus erythematosus or polyarteritis nodosa. In severe cases fever, increased erythrocyte sedimentation rates and decrease of serum albumin have been noted. In addition, pericarditis, pleurisy, pulmonary consolidation, signs of renal irritation, thrombophlebitis, peripheral neuritis, iritis and ulcers of the skin may be present. During reduction of the dose of cortisone, the appearance of a positive L.E. clot reaction as well as false-positive serologic reactions for syphilis and positive evidence for polyarteritis nodosa on biopsy has been noted in patients with rheumatoid arthritis. So far, only patients with rheumatoid arthritis (and possibly some with disseminated lupus erythematosus³²) have responded to chronic hypercortisonism by the appearance of a "panmesenchymal" and "panangiitic" reaction during withdrawal of hormone therapy.

Additional evidence of the importance of the hypercortisone state in the production of "panmesenchymal reactions" is provided by the study of Frerichs,³³ who reviewed the clinical records of all patients on whom an L.E. clot test was performed at the Mayo Clinic. The patients were divided into several groups according to their disease and the treatment received. In the group of patients with well documented rheumatoid arthritis who had never been treated with cortisone, the incidence of positive L.E. clot reactions was 5%. The same figure was found in a similar group with rheumatoid arthritis who had been treated with cortisone but showed no evidence of hypercortisonism. However, in the group of patients with rheumatoid arthritis who had been treated with cortisone and had chronic hypercortisonism, the incidence of positive L.E. clot reactions was increased to 14%. This rise was felt to be statistically significant. In those patients who were in the hypercortisone group and were undergoing withdrawal of hormone

therapy, the incidence of positive L.E. clot reactions was even greater (18%).

The most pronounced "panmesenchymal reactions" have occurred in patients with chronic hypercortisonism during withdrawal of cortisone or corticotropin therapy. None of the four patients with necrotizing arteritis in the present study was undergoing a reduction in the dosage of cortisone at the time of onset of clinical manifestations related to the arteritis, as far as can be determined. The "panmesenchymal reaction" has also been seen, however, in patients who are on large maintenance doses of cortisone, who are in the chronic hypercortisone state, and who are not undergoing a reduction in dosage at the time. It is possible that this may be due to a markedly increased demand for adrenocortical hormone because of stress-producing situations. In the face of increased need for hormone during times of stress, the normal adrenal gland responds with increased release of these substances. In the patient with chronic hypercortisonism whose adrenal cortical function has been suppressed by exogenous administration of cortisone, however, no such adjustment can take place. Suppression of adrenal cortical function has been demonstrated in these patients by low 17-ketosteroid excretion, by poor eosinophil response to corticotropin and by other signs. It is conceivable that such a situation can produce the same disproportion between need for adrenal cortical hormones and supply of them as is present when a patient is suddenly withdrawn from cortisone therapy. Thus a sudden relative deficiency of adrenocortical hormone may be produced.

In case 1, the appearance of pharyngitis on the twenty-third day of cortisone therapy was followed one week later by tonsillectomy. Fever and leukocytosis were present. It is interesting that this operative procedure preceded the appearance of a hemorrhagic skin rash and other manifestations compatible with diffuse arteritis by only 36 hours. No such clear-cut description of a stress-producing situation occurring at the time of onset of symptoms related to the arteritis could be obtained from the records of the other three patients.

Attention should be called to the high incidence of peripheral neuritis on clinical examination in the patients with necrotizing arteritis. All three patients who were seen during their terminal illness presented such findings, and in all three it was an early manifestation of the vascular disease. Also, in all three, histologic study gave ample evidence of widespread involvement of vessels in sections of peripheral nerves.

It would appear that there is no direct correlation between dosage of cortisone and the appearance of the vascular lesions described in this study. A comparison of the duration and amount of cortisone and corticotropin administration in the four patients having necrotizing arteritis and the 10 patients not having these lesions failed to show a significant difference. Many of the patients in the latter group had received just as large doses

over a comparable period as those patients in whom the vascular lesions developed. It has been pointed out²⁹ that women, and particularly postmenopausal women, are more prone to develop chronic hypercortisonism than are other patients. They seem less able to tolerate high dosages over prolonged periods without developing chronic hypercortisonism. It is interesting in this regard that both of the patients in this series with both necrotizing arteritis and hypercortisonism were postmenopausal women.

Thus it appears that the "panmesenchymal reactions" are most likely to occur in certain patients with rheumatoid arthritis who have chronic hypercortisonism. The reason for the apparently increased susceptibility of such patients to this type of reaction as compared to patients receiving cortisone therapy for other diseases is not clear at the present time.

It seems difficult to reconcile the apparent incrimination of cortisone as a causal agent in the production of necrotizing arteritis in the present study and other reports previously mentioned^{16, 17, 22-24} with the vast array of experimental and clinical evidence of the ability of adrenocortical hormones to heal or inhibit the production of these lesions. The answer to this apparent paradox may lie in the relative disproportion between supply of, and need for, adrenal cortical hormones produced in these patients.

It has been stated that there is a close association between polyarteritis nodosa, rheumatoid arthritis and other members of the so-called "collagen group" of diseases. It has been suggested that all of these diseases are but an end result of a diffuse vascular disease,³⁴ but this appears unlikely. "Fibrinoid" degeneration is a feature common to all these diseases, and histochemical studies indicate that the common feature of this fibrinoid degeneration is the precipitation of the acid mucopolysaccharide of the ground substance of the connective tissue.³⁵ This is not pathognomonic of allergy, but is a nonspecific reaction of connective tissue to injury. It is possible that necrotizing arteritis in its various forms is but an expression of the limited way in which the ground substance of connective tissue in the vascular system can react to a wide variety of insults.

In regard to the vascular lesions found in the present study, the available evidence suggests the possibility that the appearance of necrotizing arteritis in these four patients was related to the administration of cortisone. This contention is based on the following facts:

1. All four of the patients had received cortisone, and at least two showed signs of chronic hypercortisonism.
2. No widespread necrotizing vascular lesions were found in the patients who had not received cortisone.
3. Clinical experience has shown that patients with rheumatoid arthritis and chronic hypercortisonism may show evidence of a "panmesenchymal reaction," resulting in the appearance of necrotizing arteritis²⁹ and increased incidence of positive L.E. clot reactions.³⁸

SUMMARY AND CONCLUSIONS

All instances of rheumatoid arthritis examined at necropsy at the Mayo Clinic through 1954 were reviewed, with special emphasis on the incidence and character of the vascular lesions and their relationship to the administration of cortisone. There were 52 patients in the study. Fourteen of these had received cortisone and 38 had not.

Four (29%) of the group of 14 treated with cortisone had generalized lesions of polyarteritis nodosa, whereas none of the 38 patients who did not receive cortisone had such lesions.

These findings suggest that, in certain susceptible patients with rheumatoid arthritis, the administration of cortisone may precipitate the development of diffuse necrotizing arteritis.

The explanation as to why this may occur in some patients with rheumatoid arthritis treated with cortisone and apparently not in patients with other diseases (with the possible exception of disseminated lupus erythematosus) is not clear at the present time.

We found no vascular lesions specific for rheumatoid arthritis in this study.

SUMMARIO IN INTERLINGUA

Esseva examine omne casos de arthritis rheumatoide necropsiate al Clinica Mayo ante 1955, con attention special al incidentia e character de lesiones vascular e lor relation al administration de cortisona. Le studio includeva 52 patientes. Dece-quatro de illes habeva recipite cortisona, 38 non.

Quatro del 14 tractate con cortisona (29%) habeva generalisate lesiones de polyarteritis nodose. Nulle del 38 qui non recipeva cortisona habeva tal lesiones.

Iste constatationes indica possibilemente que in certe susceptible patientes con arthritis rheumatoide le administration de cortisona pote precipitar le disveloppamento de diffuse arteritis necrotisante.

Le ration pro que iste phenomeno pote occurrer in certe patientes con arthritis rheumatoide quando illes recipe cortisona durante que nihil comparabile occurre apparentemente in patientes con altere morbos (con le exception possibile de disseminate lupus erythematosus) non es clar a iste tempore.

In iste studio nos non ha trovate lesiones vascular que es specific pro arthritis rheumatoide.

BIBLIOGRAPHY

1. Curtis, A. C., and Pollard, H. M.: Felty's syndrome: its several features, including tissue changes, compared with other forms of rheumatoid arthritis, *Ann. Int. Med.* **13**: 2265, 1940.
2. Steiner, G., Freund, H. A., Leichtentritt, B., and Maun, M. E.: Lesions of skeletal muscles in rheumatoid arthritis: nodular polymyositis, *Am. J. Path.* **22**: 103, 1946.
3. Gibson, H. J., Kersley, G. D., and Desmarais, M. H. L.: Lesions in muscle in arthritis, *Ann. Rheumat. Dis.* **5**: 131, 1946.
4. De Forest, G. K., Bunting, H., and Kenney, W. E.: Rheumatoid arthritis: diagnostic significance of focal cellular accumulations in the skeletal muscles, *Am. J. Med.* **2**: 40, 1947.

5. Desmarais, M. H. L., Gibson, H. J., and Kersley, G. D.: Muscle histology in rheumatic and control cases: a study of one hundred and nineteen biopsy specimens, *Ann. Rheumat. Dis.* **7**: 132, 1948.
6. Kestler, O. C.: Histopathology of the intrinsic muscles of the hand in rheumatoid arthritis: a clinico-pathological study, *Ann. Rheumat. Dis.* **8**: 42, 1949.
7. Sokoloff, L., Wilens, S. L., and Bunim, J. J.: Arteritis of striated muscle in rheumatoid arthritis, *Am. J. Path.* **27**: 157, 1951.
8. Traut, E. F., and Campione, K. M.: Histopathology of muscle in rheumatoid arthritis and other diseases, *Arch. Int. Med.* **89**: 724, 1952.
9. Kulka, J. P., Bocking, D., Ropes, M. W., and Bauer, W.: Early joint lesions of rheumatoid arthritis: report of eight cases, with knee biopsies of lesions of less than one year's duration, *Arch. Path.* **59**: 129, 1955.
10. Christie, G. S.: The general changes in rheumatoid arthritis, in King, E. S. J., Lowe, T. E., and Cox, L. B., editors: *Studies in pathology presented to Peter MacCallum*, 1950, Melbourne University Press, Melbourne, pp. 133-143.
11. Cruickshank, B.: Focal lesions in skeletal muscles and peripheral nerves in rheumatoid arthritis and other conditions, *J. Path. and Bact.* **64**: 21, 1952.
12. Cruickshank, B.: The arteritis of rheumatoid arthritis, *Ann. Rheumat. Dis.* **13**: 136, 1954.
13. Collins, D. H.: Observations on the pathology of acute rheumatism and rheumatoid arthritis, *Ann. Rheumat. Dis.* **1**: 38, 1939.
14. Graef, I., Hickey, D. V., and Altmann, V.: Cardiac lesions in rheumatoid arthritis, *Am. Heart J.* **37**: 635, 1949.
15. Sokoloff, L., McCluskey, R. T., and Bunim, J. J.: Vascularity of the early subcutaneous nodule of rheumatoid arthritis, *Arch. Path.* **55**: 475, 1953.
16. West, H. F., and Newns, G. R.: Cortisone and rheumatoid disease, *Lancet* **2**: 1123, 1953.
17. Levin, M. H., Rivo, J. B., Scott, W., Figueroa, W. G., Fred, L., and Barrett, T. F.: The prolonged treatment of rheumatoid arthritis with cortisone and corticotropin, *Am. J. Med.* **14**: 265, 1953.
18. Nyström, G.: Associated rheumatoid arthritis, periarteritis nodosa and Felty's syndrome: report of three cases, *Ann. med. int. Fenniae* **42**: 52, 1953.
19. Ogryzlo, M. A.: Diffuse systemic rheumatoid disease (Abstr.), *Ann. Rheumat. Dis.* **12**: 323, 1953.
20. Weinberger, H. J.: Discussion of ¹⁹ and ²³, *Ann. Rheumat. Dis.* **12**: 324, 1953.
21. Ball, J.: Rheumatoid arthritis and polyarteritis nodosa, *Ann. Rheumat. Dis.* **13**: 277, 1954.
22. Finck, P. A.: Cortisone overdosage in rheumatoid arthritis: arterial and parenchymatous necroses; autopsy case report, *Arch. Path.* **60**: 374, 1955.
23. Robinson, W. D., French, A. J., and Duff, I. F.: Polyarteritis in rheumatoid arthritis, *Ann. Rheumat. Dis.* **12**: 323, 1953.
24. Bevans, M., Nadell, J., Demartini, F., and Ragan, C.: The systemic lesions of malignant rheumatoid arthritis, *Am. J. Med.* **16**: 197, 1954.
25. Baggenstoss, A. H., and Rosenberg, E. F.: Unusual cardiac lesions associated with chronic multiple rheumatoid arthritis, *Arch. Path.* **37**: 54, 1944.
26. Boyd, L. J.: The clinical aspects of periarteritis nodosa, *New York M. Coll. and Flower Hosp. Bull.* **1**: 219, 1938.
27. Rich, A. R.: The role of hypersensitivity in the pathogenesis of rheumatic fever and periarteritis nodosa, *Proc. Inst. Med. Chicago* **15**: 270, 1945.
28. Slocumb, C. H.: Relative cortisone deficiency simulating exacerbation of arthritis, *Bull. Rheumat. Dis.* **3**: 21, 1952.
29. Slocumb, C. H.: Rheumatic complaints during chronic hypercortisonism and syndromes during withdrawal of cortisone in rheumatic patients, *Proc. Staff. Meet., Mayo Clin.* **28**: 655, 1953.

30. Mainland, D.: The risk of fallacious conclusions from autopsy data on the incidence of diseases with applications to heart disease, *Am. Heart J.* **45**: 644, 1953.
31. Berkson, J.: Limitations of the application of fourfold table analysis to hospital data, *Biometrics Bull.* **2**: 47, 1946.
32. Traynor, M. V., Baggenstoss, A. H., and Slocumb, C. H.: Unpublished data.
33. Frerichs, C. T.: The L. E. cell phenomenon in rheumatoid arthritis, Thesis, Graduate School, University of Minnesota, 1954.
34. Yardumian, K., and Kleinerman, J.: Pathogenesis of so-called diffuse vascular or collagen disease, *Arch. Int. Med.* **83**: 1, 1949.
35. Altshuler, C. H., and Angevine, D. M.: Histochemical studies on the pathogenesis of fibrinoid, *Am. J. Path.* **25**: 1061, 1949.

STEROID THERAPY IN MUMPS ORCHITIS *

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MUMPS is an acute infectious disease of viral origin affecting primarily the parotid glands, but often involving the testicles, ovaries, central nervous system and pancreas. The complication of an orchitis seems confined almost entirely to adults, in whom it may constitute an exquisitely painful, disabling entity. Mumps orchitis usually appears as the parotitis is subsiding, somewhere between the fifth and seventh days. It may be unilateral or bilateral, and not infrequently is preceded by an epididymitis. The incidence of orchitis varies considerably in different series,^{1,2,3} but is generally said to be in the order of 20% of the cases of adult mumps. Occasionally an orchitis may be found without an antecedent parotitis. It is usually ushered in with severe localized pain, swelling and tenderness in the scrotum, with a marked increase in morbidity, often with chills, prostration and fever ranging from 102° to 105° F. The acute symptoms persist as a rule for three or four days, and then gradually subside over a week or more, occasionally lasting much longer. An appreciable amount of atrophy occurs in at least half of the cases, but there is a real difference of opinion as to the significance of this fact as a cause of sterility.⁴ Many months may elapse before the full effect of the mumps orchitis can be evaluated.

Treatment has varied considerably in the last few decades, but has been consistent in its relative lack of success. The patients are kept in bed with the scrotum elevated, and with applications of heat or cold. Narcotics are required for the exquisite pain invariably present. Aureomycin has been reported as effective therapy for mumps orchitis,⁵ but has proved disappointing, as is the case of all other antibiotics. Surgical measures have been carried out in many instances, with incision of the tunica albuginea in the effort to prevent pressure atrophy of the testicles.⁶ In the last few years several authors have tried a more conservative approach for prophylaxis and treatment of epididymo-orchitis, using pooled normal plasma and gamma globulin from convalescent mumps serum.⁷ Diethylstilbestrol has been used extensively in an effort to prevent the complication of mumps orchitis. The results have been inconclusive, and Norton⁸ found no significant difference in the treated patients and those in the control groups. He concluded that the administration of diethylstilbestrol does not prevent the onset of orchitis due to mumps, although he felt that it may decrease the fever and degree of

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orchitic swelling. It was of practical interest that he did not find any significant difference in the incidence of epididymo-orchitis in patients confined to bed and those permitted to walk about during convalescence.

In 1954, the first report appeared concerning the use of steroid therapy in mumps orchitis. Solem⁹ reported six cases in which corticotropin was given. In five there was prompt subsidence of the acute inflammatory involvement of the testes after a single injection of Cortico-Depot, Nyco 100 I. U. He felt that the beneficial effects could be attributed to the blockage of the exudative tissue reaction with a reduction of the cellular inflammation. It was suggested that this favorable effect might well prevent subsequent disturbances of spermatogenesis.

Recently, the authors have had experience with the use of steroids in four cases of mumps orchitis, with favorable results. When it became apparent that this form of therapy was not of common knowledge, it seemed worth while to report them briefly.

CASE REPORTS

Case 1. A 37 year old physician had a history of mumps at the age of eight, and had served on a mumps ward in the Navy. Despite this apparent immunity, he developed a typical mumps parotitis after intimate exposure to his three children suffering from the same disease. Diethylstilbestrol was taken in an effort to prevent complications. However, on the fifth day he developed chills, fever, malaise and severe pain in the right testicle. This was followed by typical signs of an acute epididymo-orchitis, with marked edema and subsequent development of a similar lesion on the left side on the following day. There was suggestive evidence of encephalopathy, with slight mental confusion and meningismus. He was started on hydrocortisone, 20 mg. four times a day on the second day of his illness. There was a prompt, dramatic response in the lessening of edema and pain in the testicles, with equally impressive subsidence in the fever and systemic effects. Medication was discontinued after five days. Subsequent studies a year after the illness revealed slight atrophy of the right testicle, considerably less than is usually encountered in comparable degrees of severe involvement.

Case 2. A 27 year old insurance salesman was seen on the seventh day of his illness with mumps contracted from his young son. For 24 hours he had complained of chills, fever and malaise accompanying marked swelling and pain in his right testicle. Examination revealed a subsiding bilateral parotitis and an exquisitely tender, swollen right testicle. He was started on oral prednisone, 5 mg. four times daily, with a prompt subsidence in both local and systemic manifestations in less than 48 hours. An uneventful recovery ensued, and there was no evidence of testicular atrophy six months later.

Case 3. A 19 year old college student was seen on the sixth day of a typical mumps parotitis complaining of chills and fever, with severe pain, swelling and tenderness in his right testicle. Physical examination revealed evidence of a subsiding unilateral parotitis and marked edema and tenderness of a right-sided orchitis. He was started on 5 mg. of prednisone by mouth four times daily, but developed evidence of an orchitis on the left side the following day. However, this involvement was much less severe than on the original side. Prompt subsidence of local and systemic manifestations was evident in 48 hours, and the subsequent recovery was uneventful and without testicular atrophy.

Case 4. A 50 year old pipeline worker was seen eight days after onset of acute bilateral parotitis. For the three preceding days he had been seriously ill, with severe headache, vomiting, intermittent hiccups, a daily temperature elevation up to 103° F., and acute bilateral orchitis. Treatment was begun with 20 mg. of ACTH intramuscularly every six hours. At the end of 24 hours he was afebrile and asymptomatic. The swelling of the testicles subsided within 48 hours. The ACTH was continued in decreasing dosage for a total of three days, when it was discontinued. The convalescence subsequently was uneventful.

DISCUSSION

Inasmuch as mumps orchitis has a self-limited course, one might be tempted to speculate that the use of steroids was unnecessary, or that the ensuing response represented the natural resolution of the pathologic process. However, when the results in this limited series are compared with the experience of one of the authors in the average course of a large series of mumps orchitis in a Naval infectious disease ward, the response to steroids is found to be quite dramatic. Kinsell¹⁰ states that at least three non-hormonal factors are concerned in the over-all picture of resistance to infectious disease. First is the inflammatory reaction, which may be considered as an initial line of defense, localizing the organism until the production of specific immune bodies has gathered sufficient momentum. Inflammation is profoundly inhibited by pharmacologic amounts of corticoids. In the case of mumps orchitis, such a reaction is desirable to reduce the edema and vascular blockage attending the exudative tissue reaction. The second nonhormonal factor consists of the production of specific immune bodies which overwhelm the invading organisms or neutralize toxins, giving temporary or permanent protection. There is no evidence that corticoids in therapeutic amounts interfere with antibody formation. This fact would seem of practical importance in mumps orchitis, as it would be unwise to alter the subsequent permanent immunity normally engendered. The present use of gamma globulin is an example of temporary limited immunity in this disease. The third nonhormonal factor, according to Kinsell,¹⁰ consists of antibiotics. These agents are so effective in dealing with many of the infectious organisms that the development of an inflammatory response and the antibody reaction become of secondary importance. However, the effectiveness of antibiotics in mumps orchitis has been uniformly disappointing. To an increasing degree, however, steroids are being used in conjunction with antibiotics in severe infections to gain time while awaiting specific effects. This principle limits the use of steroids to infectious agents for which specific antibiotics exist. A notable exception, however, is found in the use of corticoids in viral hepatitis, particularly in the presence of hepatic coma, where the discontinuance of this form of therapy may cause relapse.¹¹ A second exception is noted by Kinsell,¹⁰ who states that "intensive corticoid therapy for patients with mumps orchitis appears to be consistently associated with rapid and complete disappearance of all in-

flammation in the gonads. If therapy is instituted sufficiently early, it is probable that there will be no residual damage to the testes. No untoward effects have been observed." Beeson¹² has recently commented on his experience with ACTH and cortisone in six cases of mumps orchitis. He felt that this therapy should be employed routinely as a symptomatic measure, but believed that it remains to be determined if such therapy will reduce the incidence of subsequent atrophy and sterility. The authors recently had an interesting experience in the treatment of a case of mumps pancreatitis. The patient had had a prolonged course of a persistent parotitis and pancreatitis, with amylase levels over 1,400. A dramatic reduction in the serum amylase and systemic effects was produced by steroid therapy in 48 hours, followed promptly by a relapse with discontinuance of medication. Reinstitution of therapy was characterized by a prompt remission, remaining permanently after one more week of corticoid administration. Eskwith¹³ reported a dramatic response to steroid therapy in a case of acute hemorrhagic pancreatitis of the usual etiology. It would seem justifiable to employ these agents in mumps pancreatitis and probably in hemorrhagic pancreatitis in the absence of infection.

In view of the experience recounted, it is the opinion of the authors that steroid therapy should be promptly instituted in all cases of mumps orchitis. Such measures will greatly reduce the severity of this painful, disabling entity and probably will reduce the degree of atrophy, potential sterility and possible hypogonadism. It is interesting to speculate that the prompt use of corticoids in mumps parotitis in adult males may even prevent the complication of an orchitis or pancreatitis.

SUMMARY

Four cases are presented of mumps orchitis treated by steroid therapy. A rapid remission was noted in all cases, with a dramatic reduction in the local inflammation as well as generalized systemic effects. It is suggested that all cases of mumps orchitis be treated promptly with steroids except in the presence of the usual unrelated contraindications to this form of therapy.

SUMMARIO IN INTERLINGUA

Orchitis es un complication dolorose e invalidante de parotitis. Illo occurre in circa 20% del patientes adulte afficite per iste morbo. Atrophia testicular resulta in circa 50% del patientes con orchitis parotidee, sed le autoritates non es de accordo in re le importantia de iste typo de atrophia testicular como factor causative in le disveloppamento de sterilitate.

In le passato le tractamento de orchitis parotidee esseva generalmente paucio satisfactori. Antibioticos, plasma de banca, globulina gamma, diethylstilbestrol, e incision del tunica albuginee—omne iste mesuras se ha provate disappunctante.

In 1954 Solem reportava sex casos de orchitis parotidee tractate con corticotropina. In cinque de istos, un prompte subsidentia del acute inflammation testicular esseva notate.

Le autores reporta le casos de quatro pacientes de orchitis parotidee qui esseva tractate con ACTH o steroides adrenal. In omnes le inflammation testicular e le manifestationes systemic subsideva intra 48 horas. Le periodos de tractamento variava inter tres e cinque dies. Nulle reactiones adverse esseva notate. In un del pacientes leve grados de atrophia testicular esseva notate un anno plus tarde. In duo casos nulle atrophia testicular occurreva. In le quarte patiente nulle observation consecutori esseva obtenite.

ACTH esseva administrate a un del pacientes in un dosage initial de 20 mg per via intramuscular omne sex horas. Le medication esseva continuate in doses decrescende durante un periodo de tres dies. Hydrocortisona esseva usate in un secunde patiente in un dosage de 20 mg per via oral quatro vices per die durante cinque dies. Prednisona esseva usate in le tertie e le quarte caso in un dosage de 5 mg per via oral quatro vices per die durante cinque dies.

Le tractamento de orchitis parotidee con ACTH o steroides adrenal resulta apparentemente in un prompte alleviation del manifestationes local e systemic de iste vexante condition. In plus, il pare possibile que iste typo de tractamento es etiam capace a prevenir le occurrentia de atrophia testicular e sterilitate.

BIBLIOGRAPHY

1. Worden, E. M.: Mumps, *Canad. M. A. J.* **50**: 47, 1944.
2. Dermon, H., and Lettew, E. W.: Mumps, *Am. J. M. Sc.* **208**: 240, 1944.
3. Cecil, R. L.: Textbook of medicine, 9th Ed., 1955, W. B. Saunders Company, Philadelphia.
4. Ballew, J. W., and Masters, W. H.: Mumps: cause of infertility: Fertility and Sterility **5**: 536, 1954.
5. Spinelli, N. P. R., Cressy, N. L., and Runkel, P.: Aureomycin in the treatment of mumps orchitis and encephalitis, *Connecticut M. J.* **15**: 113, 1951.
6. Wesselhoeft, C., and Vose, S. N.: Surgical treatment of severe orchitis in mumps, *New England J. Med.* **227**: 297, 1942.
7. Gellis, S. S., McGuinness, A. C., and Peters, M.: A study on the prevention of mumps orchitis by gamma globulin, *Am. J. M. Sc.* **210**: 661, 1945.
8. Norton, R. J.: Use of diethylstilbestrol in orchitis due to mumps, *J. A. M. A.* **143**: 172, 1950.
9. Solem, J. H.: The effect of corticotropin in the orchitis of mumps, *Acta med. Scandinav.* **149**: 341, 1954.
10. Kinsell, L. W., and Jahn, J. P.: Combined hormonal-antibiotic therapy in patients with fulminating infections, *Arch. Int. Med.* **96**: 418, 1955.
11. Johnson, E. C., and Bennett, H. D.: ACTH in the treatment of infectious hepatitis, *Gastroenterology* **28**: 265, 1955.
12. Yearbook of Medicine, P. B. Beeson, Editor, 1955-56, Year Book Publishing Company, Chicago, p. 63.
13. Eskwith, I. S., Cacace, V. A., and Sollosy, A.: Acute hemorrhagic pancreatitis, *New England J. Med.* **252**: 494, 1955.

ATYPICAL SYNDROMES IN HYPERTHYROIDISM *

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UNRECOGNIZED hyperthyroidism may progress insidiously to an advanced phase of the disease. The atypical syndromes disguising the true nature of the process are varied, with manifestations related to other organ systems diverting attention from the underlying metabolic disturbance. The variations in the clinical picture may frequently lead to errors in diagnosis when their nature remains obscure. Virtually any organ or system may present abnormalities simulating primary disease within it as a result of the adverse influence of hyperthyroidism upon its function.

Among cases which have been found to produce considerable difficulty in diagnosis are those with involvement of the cardiovascular system. Congestive heart failure, cardiac arrhythmias and hypertension have each been treated for long periods without discovery of the underlying thyrotoxic process. In other patients the influence of the disease upon cerebral functions may produce severe anxiety states, psychosis or encephalopathic manifestations, concealing the basic disease. Many other variations, mimicking osteoporosis, gastrointestinal disease and acute abdominal states, rheumatic states, myasthenia gravis, edema and albuminuria, have been observed. Confusion may frequently develop in the diagnosis of thyrotoxicosis when one of the following atypical findings is observed: (1) normal or slow pulse rate; (2) progressively increasing weight and obesity; (3) absence of a palpable thyroid gland; (4) apathetic demeanor of the patient, or (5) absence of apparent hypermetabolism with normal metabolic rate. Our experience in the Thyroid Clinic of Temple Hospital has provided examples of each of these conditions which have led to delay in the diagnosis of hyperthyroidism. It is our purpose to review the clinical aspects of several examples of these syndromes and atypical cases, and to emphasize the necessity for a constant awareness for the variations of thyrotoxicosis described.

The ultimate diagnosis of thyrotoxicosis in these and in more conventional cases is established by laboratory studies and clinical appraisal of the total patient. However, it is clinical acumen which is essential and which supersedes the laboratory in formulating the suspicion of thyroidal disease in the overwhelming majority of cases, whether typical or atypical. It is principally in borderline hyperthyroidism that the laboratory aids are least useful. In the type of patient under discussion, the uptake and release of I^{131}

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are elevated, as is the serum precipitable iodine level. The reduction of I^{131} uptake following thyroid or tri-iodothyronine administration, seen in the normal subject, is absent in patients with thyrotoxicosis. The serum cholesterol values are usually reduced below the patient's normal levels. The basal metabolic rate is usually elevated above the patient's own average, but rarely may fall within the normal range. An often unrecognized feature is that of anemia, usually mild, but occasionally of clinical significance, of the hypochromic type. The application of the newer technics of laboratory study has greatly aided the recognition of the atypical hyperthyroid syndromes.

CASE REPORTS

Case 1. Thyrotoxicosis, heart failure, slow pulse rate, gastric symptoms: A 58 year old white male developed manifestations of progressive dyspnea with effort limitation and ankle edema. A diagnosis of congestive heart failure due to arteriosclerotic heart disease was made, and digitalis was administered for a period of seven months, without benefit. It is notable that clinical symptoms of coronary artery insufficiency were absent, although the electrocardiogram disclosed evidence of an old posterior myocardial infarct.

Digitalis and cardiac therapy were discontinued without change in the patient's clinical status. Prior to admission he had developed nausea and burning eructations. On examination the pulse rate was 70 per minute; blood pressure, 112/90 mm. of Hg. The thyroid gland was diffusely enlarged. A staring expression and fine tremor of the fingers were observed. The serum cholesterol was 146 mg.%. The basal metabolic rate was plus 70%. He was treated with antithyroid drugs in preparation for subtotal thyroidectomy. Within six weeks the basal metabolic rate was plus 23%, and most of the thyrotoxic symptoms had subsided. Within a period of three months of antithyroid medication the basal metabolic rate was minus 12%, and all manifestations of effort dyspnea, nausea and tremor had disappeared.

Comment: The occurrence of relative bradycardia is exemplified by this case of a patient with congestive heart failure unresponsive to cardiac therapy. Organic myocardial damage evidenced by the electrocardiogram, may have involved the focus of impulse formation, making it resistant to the usual acceleration seen in thyrotoxicosis. Failure of thyrotoxic heart disease to respond to cardiac therapy over a seven month period, with a rapid recovery on antithyroid medications, is a common clinical observation. Failure to recognize thyroidal disease might have led to fatal congestive failure. Nausea and flatulence persisted for weeks after cessation of digitalis but disappeared upon the return to euthyroid status. Abdominal symptoms are encountered in patients with severe forms of thyrotoxicosis consisting of nausea and anorexia. Vomiting may occur in association with diarrhea in patients with impending crisis.

Case 2. Acute abdominal pain, auricular fibrillation, precordial pain in thyrotoxicosis: A 32 year old white female was admitted to the hospital with symptoms of pain in the right upper quadrant of 24 hours' duration. She had previously experienced vomiting of five days' duration, associated with weakness and diffuse aches

and pains. Examination disclosed cardiac enlargement with rapid auricular fibrillation. Mitral valvular disease was suspected on the basis of clinical findings. The thyroid gland was diffusely enlarged. The eyes were prominent and staring; lid lag was observed. Marked tremor and nervousness were present. In the right upper abdominal quadrant a palpable mass was noted which was tender to palpation. Cholecystitis was diagnosed initially, and the patient was transferred to the surgical service. However, the acute toxic manifestations of the patient suggested thyroid storm. The protein-bound iodine was $18.5 \mu\text{g}$; the basal metabolic rate was plus 44%. Chest roentgenogram revealed enlargement of the heart with mitral configuration and left ventricular enlargement. The serum cholesterol was 98 mg. per 100 c.c. The patient was treated with propylthiouracil on the basis of probable thyrotoxicosis. Within a period of two weeks marked improvement was observed. The nervousness and tremor subsided. The pulse rate slowed to 88 per minute; the auricular fibrillation was readily converted to sinus rhythm with quinidine. The heart size reverted to normal, with no sign of auricular enlargement. The basal metabolic rate was reduced to plus 15%, and the serum cholesterol rose to 145 mg. per 100 c.c. The palpable liver disappeared, and right upper quadrant tenderness could not be elicited. Treatment with propylthiouracil was continued, with an obvious favorable response. Subtotal thyroidectomy was planned for definitive management of thyrotoxicosis.

Comment: The roentgen appearance of mitral stenosis with prominence of the pulmonary artery segment has been described repeatedly in patients with thyrotoxicosis. An increase in the intensity of the first mitral heart sound associated with a systolic murmur may also occur. These findings in the thyrocardiac patient may lead to an erroneous diagnosis of mitral valvular disease, as in the present case.

Abdominal pain in thyrotoxicosis has simulated a variety of acute surgical emergencies.¹ In this instance a typical picture of cholecystitis was presented and arrangements for gall-bladder surgery were instituted. The recognition of thyrotoxicosis led to appropriate treatment and correction of the condition. The mechanism of abdominal pain in this instance and of the palpable, tender mass in the right upper quadrant may have been acute enlargement of the liver due to congestion. The importance of abdominal pain in thyrotoxicosis is apparent, just as it is in diabetic acidosis, hypoparathyroidism and adrenal insufficiency.² Unnecessary and hazardous surgical intervention must be avoided in these cases. Localized pain simulating peptic ulcer, cholelithiasis or appendicitis is not rare; the differential diagnosis is difficult and most important.

Case 3. Congestive heart failure: A 35 year old male was referred to the thyroid clinic with a history of severe dyspnea, orthopnea and edema of the lower extremities. The symptoms had begun 18 months previously while the patient was working as an automobile mechanic. Nervousness, palpitation and effort dyspnea were noted at this time and became progressively more severe. Upon failure to improve on cardiac therapy he moved to the West Coast to work under more agreeable climatic conditions. Here again, he was treated for the increasingly serious symptoms of congestive heart failure, without benefit. At this time he became incapacitated and was forced to move East to be cared for by relatives. Examination disclosed evidence of moderate weight loss, nervousness and tremor. There was an absence of the eye signs of thyrotoxicosis. The neck veins were distended; the skin was warm, but sweating

was absent. A forceful cardiac impulse was palpable near the left anterior axillary line. The pulse rate was 104 per minute; the blood pressure was 144/70 mm. of Hg. Basal pulmonary râles and grade I pitting edema of the legs were noted. The thyroid gland was slightly enlarged to palpation and a faint bruit was audible; no nodules were present. The basal metabolic rate was plus 64%. Serum cholesterol was 136 mg.%. The radioactive iodine uptake was 68%, with a conversion ratio of 73%. Chest x-ray revealed generalized cardiac enlargement. The electrocardiogram disclosed sinus tachycardia with lowering of the voltage of the T waves. Treatment with radioactive iodine by Dr. R. Robbins was administered on the basis of the diagnosis of thyrotoxic cardiac disease with congestive failure. Prompt improvement followed over a period of four weeks upon administration of 7.7 mc. of I^{131} . Subsequently, all manifestations of cardiac abnormality disappeared. The heart size reverted to normal, as did the electrocardiogram. This patient has remained well and has returned to his former occupation.

Comment: About 20% of the thyrocardiac patients have no evidence of underlying organic heart disease. The remainder have hypertensive or arteriosclerotic cardiac involvement which is incapable of supporting the increased metabolic demands imposed by hyperthyroidism. The cardiac output in the thyrotoxic patient is elevated to a level corresponding to that of the normal subject undergoing strenuous activity. Upon physical effort there is a disproportionate rise in cardiac output, achieved principally by an increase in pulse rate. The high level of cardiac output serves to maintain the tissue requirements for metabolic substrates and oxygen. The increased rate of circulation in hyperthyroidism results in an elevated venous return. The circulation time is typically decreased to 7 to 10 seconds and remains normal in the presence of heart failure. Vasodilatation and rapid blood flow aid in the dissipation of heat from the body.

The diagnosis of thyrocardiac disease is not difficult when typical manifestations of hyperthyroidism are in evidence. However, in some instances the findings of heart failure may obscure the underlying metabolic disorder. Thyrotoxic cardiac disease should be suspected in the presence of paroxysmal or persistent auricular fibrillation, in patients with unexplained tachycardia persisting under sedation or during sleep, in those with cardiac disease of unknown origin, and in those with congestive failure not responding to conventional therapy.³ Careful examination must be conducted to detect such findings as a staring expression, warm, moist skin, rapid weight loss, wide pulse pressure, and a fine tremor of fingers or tongue. The diagnosis of this and other types of thyrotoxic complications in problematic cases may be best established by the use of a clinical trial of iodine or Tapazole. Amelioration of symptoms in previously unresponsive heart disease may occur within a period of 14 days on such treatment. In these cases we prefer definitive treatment with radioactive iodine or surgery to prolonged medical therapy with antithyroid compounds.

Case 4. Localized edema of eyelids in thyrotoxicosis: Three years ago a 38 year old male noted transient swelling of the eyelids associated with nervousness and loss of weight. During the four months prior to admission the circumocular

edema had been constant. Examination revealed a hyperkinetic, somewhat emaciated patient with moist, warm skin. None of the eye signs of thyrotoxicosis was present; the fundi were normal. Extensive edema of the lids was observed, especially over the lower palpebrae. The lid margins and conjunctivae were normal. The swelling of the lids was nonpitting. The thyroid gland was not palpable. The cardiovascular system was normal; the resting pulse was increased to 92 per minute. A fine tremor was observed in the outstretched fingers. The initial basal metabolic rate was plus 61%. A clinical trial of Lugol's solution (compound solution of iodine) was instituted. After three weeks of treatment all signs of thyrotoxicosis had disappeared and a 14 pound weight gain was observed. The basal metabolic rate was reduced to plus 10%. The eyelid edema had entirely subsided. The patient refused preparation for surgery and was referred for further treatment to the outpatient clinic where, during a lapse of therapy, the signs of thyrotoxicosis appeared and marked periorbital edema returned.

Comment: The significant features of this case were the development of marked eyelid edema and the absence of a palpable thyroid gland in the presence of severe thyrotoxicosis. The cardiac, renal and biochemical findings failed to explain the edema. No history of allergy was elicited. With antithyroid medication and improvement in the patient's metabolic status, the signs of thyrotoxicosis disappeared and simultaneously the edema rapidly cleared. Subsequently, when treatment was withheld, the edema recurred and hyperthyroid symptoms reappeared.

The occurrence of edema in hyperthyroidism has been reported most frequently in connection with thyrocardiac complications. However, transitory localized edema of nonpitting variety of undetermined cause has been described occasionally. Best known of the latter type is the localized pretibial myxedema. We have at present three patients under treatment for thyrotoxicosis with this complication. Each of these has some degree of ophthalmopathy. Two have received radioactive iodine therapy and one had a subtotal thyroidectomy. The type of edema described in this connection may be classified as localized myxedema of the palpebrae, although the precise nature of the swelling has not been proved. There was no evidence of proptosis or involvement of the retro-orbital tissues.

Case 5. Chronic thyrotoxic encephalopathy and convulsive state: A 23 year old female was admitted in a semicomatose state to the neurosurgical service of Temple University Hospital in May, 1954. The history provided by her husband revealed a rapid appearance of symptoms of nervousness, irritability and weight loss. A basal metabolism test performed by her local physician was plus 49%. At this time, approximately 10 months prior to her admission, she experienced a severe generalized convulsive seizure, followed by deep stupor of two days' duration. The generalized convulsive episodes became increasingly more frequent despite treatment with Itrumil. She became disoriented and confused, with longer periods of coma. Because of her failure to respond to the antithyroid therapy and the convulsive disorder, the presence of a brain tumor was suspected.

Examination revealed an asthenic, poorly nourished patient unresponsive to questions and various stimuli. Funduscopic examination was normal; eye signs of thyrotoxicosis were absent. The thyroid gland was diffusely enlarged to about three times normal size; no abnormal masses were palpable. Generalized tremulousness and spasticity were noted; muscle atrophy was apparent. The heart and lungs were

normal; the pulse rate was 106 to 180 per minute throughout her hospitalization of four months. The neurologic examination was entirely normal. The spinal fluid pressures on several occasions were elevated to 200 mm. of water; spinal fluid protein ranged from 83.6 to 100 mg.%. Radioactive iodine uptake was 51%, with a 24 hour conversion ratio of 83.5%. The basal metabolic rate could not be determined because of technical difficulties.

To exclude the possibility of brain tumor, bilateral cerebral angiography was performed, with negative results. Following these studies, a pneumoencephalogram was performed which disclosed a normal ventricular pattern. An acute exacerbation of the thyrotoxic process in the form of thyroid crisis occurred during the latter procedure. The temperature rose from levels of 100° F. to 105° F., and the pulse rate rose to 180 per minute. Treatment with glucose solution, hydrocortisone and sodium iodide intravenously, followed by large doses of Tapazole, controlled the critical complication. Intensive antithyroid management was continued with Lugol's solution (compound solution of iodine) and Tapazole thereafter. Dilantin and phenobarbital were given to suppress the convulsive disorder, which appeared frequently during hospital observation. The electro-encephalogram disclosed only diffuse cerebral impairment; x-rays of the skull and chest were normal. During the prolonged hospitalization the patient was fed a high caloric formula by nasogastric tube and received oxygen therapy intermittently.

After four months the patient gradually became more alert, convulsions disappeared, and manifestations of thyrotoxicosis diminished. She was discharged receiving Lugol's solution (compound solution of iodine) and Tapazole; Dilantin and phenobarbital were continued for their anticonvulsant effect. The latter agents were withdrawn over a period of several months, with no recurrence of convulsions. In May, 1955, the antithyroid compounds were discontinued. Two weeks later a radioactive iodine uptake study was found to be 81%, with a conversion ratio of 93%. The patient was given 7.7 mc. of radioactive iodine in treatment of thyrotoxicosis by Dr. R. Robbins. Within one month she was remarkably improved, and all manifestations of hyperthyroidism had disappeared. Four months later the patient became pregnant, with no recurrence of any of her previous symptoms.

Comment: We have observed three patients with chronic thyrotoxic encephalopathy. The other two cases were less dramatic than that described, with briefer periods of disorientation and stupor and without convulsive seizures. One of these patients was prepared for surgery, during which he developed an acute thyroid crisis controlled promptly with intravenous hydrocortisone and iodides. The encephalopathic type of thyrotoxicosis has been described by Zondek as "Coma Basedowicum."⁴ However, relatively few clinical descriptions of this condition appear in the medical literature. Chapman and Maloof⁵ have recently reported three additional patients manifesting this syndrome, one of whom had convulsive attacks. The cerebral type of hyperthyroidism apparently develops in patients having a relatively rapid and progressive toxic process. The patients are initially extremely restless and hyperkinetic, with periods of excitation. This picture gives way to a semistuporous and apathetic demeanor, with loss of expression and development of spasticity of the limbs. As coma supervenes, the patients manifest marked weakness and muscle wasting. The complete recovery of our patients following appropriate therapy with I¹³¹ or subtotal thyroidectomy suggests that the cerebral changes

responsible for this condition are functional rather than organic in nature. No effect of hyperthyroidism of the noncomatose type upon cerebral blood flow or oxygen utilization has been observed in the report of Scheinberg.⁶ However, these studies have not been performed in patients with the encephalopathic syndrome.

While it may be assumed that thyrotoxic encephalopathy is produced by the abnormal metabolic effects of hyperthyroidism upon cerebral tissues, there is no actual information available on this point. Clinical observations have been reported on the converse relationships, however, in which cerebral injury has resulted in thyrotoxicosis. A well known example of this is carbon monoxide poisoning, which may damage the midbrain centers, following which thyrotoxicosis may appear. Encephalitis and brain concussion may produce the same effects. In the three cases observed here no history or findings suggestive of a cerebral injury could be elicited.

Case 6. Myasthenia gravis and toxic thyroid nodule: A 37 year old married female was admitted to the hospital with a history of progressive weight loss and weakness following her third successful pregnancy six months previously. Increasing irritability, nervousness and occasional depression developed during this period. Examination disclosed evidence of weight loss and weakness. A nodule was palpable within the isthmus of the thyroid gland. The basal metabolic rate was plus 28%. Lugol's solution (compound solution of iodine) was administered for a period of two weeks, after which the basal metabolic rate declined to plus 18%. The anticipated improvement in the clinical manifestations of thyrotoxicosis was not observed. The patient continued to complain of weakness; she developed ptosis of the eyelids, dysphagia and dysarthria. During a menstrual cycle it was noted that the latter symptoms were aggravated. Prostigmin given intramuscularly resulted in marked alleviation of symptoms. On the basis of clinical developments and response to Prostigmin, a diagnosis of myasthenia gravis complicating thyrotoxicosis was made. Treatment with Prostigmin was successful during the next several months, when the patient became pregnant. It was necessary to increase the dosage of Prostigmin during pregnancy, due to the aggravation of symptoms, despite the continued administration of antithyroid medication.

Comment: The coexistence of myopathic syndromes and thyrotoxicosis has been recorded frequently in recent years. Most commonly in these cases there are marked muscle weakness and atrophy of insidious onset in patients who may have an apathetic form of thyrotoxicosis when seen by the physician. The process affects the proximal muscles of pectoral and pelvic girdles. One of our patients with this syndrome had to go up one flight of stairs in her home on hands and knees, with intervals of rest during the trip. Another common myopathic syndrome is that of exophthalmic ophthalmoplegia. Degeneration of the muscle fibers, with edema and cellular infiltration, is seen pathologically, resulting in weakness of the ocular muscles.

Myasthenia gravis differs from thyrotoxic myopathy in that the bulbar and ocular muscles are predominantly involved; there is rapid fatigability of muscles, with absence of obvious atrophy. The beneficial effects of

Prostigmin and the deleterious influence of curariform agents are useful as diagnostic tests. In the reported cases of combined myasthenia gravis and thyrotoxicosis, no definite relationship between the onset of the two diseases in the patient has been established. Nonsurgical treatment is recommended because of the high mortality rate associated with surgery in these patients. Treatment of thyrotoxicosis has been found to lessen the severity of the myasthenia and to improve the response to Prostigmin.

DISCUSSION

The occurrence of atypical syndromes in hyperthyroidism is of extreme importance, since they frequently result in an error in diagnosis when their nature is not recognized. In these patients the characteristic features of thyrotoxicosis are overshadowed by other prominent physical findings, thus diverting attention from the possibility of an underlying metabolic disturbance. There are many systemic effects related to excessive thyroxine secretion, which have been extensively studied. These effects involve the cardiovascular, gastrointestinal, cerebral, neuromuscular, hepatic, renal and osseous structures. The clinical manifestations of thyrotoxicosis may be specifically related to any one or several of these systems, due to the influence of the hormone upon their function.

The circulatory disturbances observed in hyperthyroidism are capable of producing clinical findings apparently arising primarily from the cardiovascular system. The development of tachycardia, dyspnea, orthopnea and edema may lead to the diagnosis of congestive heart failure in these patients. In approximately two thirds of the thyrotoxic patients with cardiac decompensation, underlying heart disease has been demonstrated. In the remaining groups no preëxisting cardiac pathology can be shown at autopsy, or evidenced upon recovery from the thyrotoxic cardiac disturbance. The incidence of signs of congestive heart failure has been observed to be approximately 15% in patients with hyperthyroidism. This complication occurs most frequently in those who have had the disease over longer periods and in older patients, although two of our patients were less than 35 years of age. In any given case, cardiac failure develops on the basis of two factors: the demands for increased cardiac work, and the capacity of the myocardium to perform the required work. The frequent occurrence of auricular fibrillation suggests an altered state of myocardial performance in thyrotoxicosis. The heart in this disease shares in the general increase in oxidative activity; a decrease in glycogen and high energy phosphate compounds, adenosine triphosphate and creatine phosphate has been reported in the experimental thyrotoxic heart. It is probable that thyrotoxicosis may produce cardiac distress because of the inability of the heart, laboring under the lowered concentration of available energy, to meet the demands of the general increased metabolism.

In the majority of patients with the combined conditions of hyper-

thyroidism and heart failure, the two diagnoses are apparent. However, angina pectoris, auricular fibrillation and congestive failure may occur as predominant manifestations. Careful examination is necessary to detect the characteristic findings of thyrotoxicosis. The diagnosis is vital in the proper management of these patients. Therapeutic trials are justified in substantiating the existence of the metabolic disturbance causing the cardiac ailment.

The function of the gastrointestinal tract is significantly affected by the hormone. Thyroxine is the only agent which increases the rate of absorption; it also increases the rate of intestinal motility and depresses secretory activity of the gut. Diarrhea is a most common symptom in thyrotoxicosis; nausea and vomiting are more unusual, and occur only in the more severe stages of the process. Abdominal pain simulating gall-bladder disease, appendicitis, ulcer or colitis is not uncommon and may produce a serious diagnostic dilemma. The recent studies concerning liver function and morphology in thyrotoxicosis have disclosed few changes other than moderate decreases in liver glycogen and minor alterations in hepatic function tests. The abnormalities which have been observed are readily reversible in nearly all instances upon establishment of euthyroidism. The hepatic alterations cannot be correlated with the severity of the metabolic derangement, and may be associated with nutritional deficits which have developed during the illness.

The problem of psychoneurotic or psychotic behavior in the thyrotoxic patient has been of interest, although there is little information as to the mechanisms involved in the influence of the thyroid upon cerebral function. The prominence of mental symptoms in some of the patients is such that the underlying endocrine disorder is overlooked. In these cases there is often a prior history of emotional instability, so that consideration has properly been accorded to the possibility that thyrotoxicosis may evolve through pathways emerging from cerebral centers by way of the hypothalamus to the pituitary. However, the overt manifestations of abnormal emotional patterns or the toxic psychosis observed in these patients frequently fades with the prompt treatment of hyperthyroidism. Although careful psychiatric scrutiny may still reveal the presence of emotional instability after adequate antithyroid treatment, remarkable recoveries from these manifestations are generally observed.

Among other conditions which may lead to a delay in the diagnosis of thyrotoxicosis are diabetic coma and osteoporosis. Where complications are attended by symptoms of such severity, only careful re-appraisal of the situation permits the proper recognition of the associated hyperthyroidism.

SUMMARY

Patients with hyperthyroidism are described whose presenting signs and symptoms were referable to one organ system: cardiovascular, gastroin-

testinal or central nervous systems. Since the usual signs of hyperthyroidism were lacking, they were treated unsuccessfully for months without the suspicion arising that the real trouble was an overactive thyroid gland. Careful, painstaking scrutiny of the total patient, aided by appropriate laboratory studies, revealed the underlying thyrotoxicosis, and proper treatment brought about amelioration of symptoms and complete recovery.

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SUMMARY IN INTERLINGUA

Le pronunciate tableau clinic de thyrotoxicosis es facile a diagnosticar. Tamen, il existe patientes qui suffre de iste condition in un forma con manifestationes que simula morbos de certe systemas de organos in le sphaera del influenza thyroide como per exemplo le systema cardiac, gastrointestinal, o nervose central. Isto pote resultar in errores diagnostic o in non-responsa al therapia, si le subjacente thyrotoxicosis non es recognoscite e appropriatemente tractate.

Es presentate le caso de un patiente con disfallimento cardiac, bradycardia, e disturbanceles gastric. Durante septe menses ille esseva tractate, sin beneficio, pro primari morbo de corde discompensate. Post le constatacion de un basse nivello de cholesterol sanguinee (146 mg%) e un alte metabolismo basal (plus 70%), le therapia cardiac esseva interrompita e un medication antithyroide esseva prescribe. Intra un periodo de tres menses omne signos e symptomatas de disfallimento cardiac se clarificava, e le metabolismo basal descendeva a minus 12.

Un simile caso esseva tractate durante 18 menses, sin ulle successo, pro recalitrante morbo cardiac. Post le constatacion de un metabolismo basal de plus 64% e un acceptation de iodo radioactive de 68%, le patiente recipeva 7,7 mc de I^{131} . Sequeva melioration in le curso de quatro menses, con disparition subsequente del manifestationes de congestive disfallimento cardiac.

Patientes de hyperthyroidismo pote exhibir acute attackos de vomito e dolor abdominal, que pote esser interpretate como effecto de un acute lesion chirurgic intra-abdominal. Un tal caso con symptomatas abdominal de acute cholecystitis es describe. Le recognition del subjacente thyrotoxicosis e le tractamento con propylthiouracil resultava in un marcate melioration del signos clinic e laboratorial. Assi le risco de un non-necessari operation exploratori esseva evitate.

Le typo cerebral de hyperthyroidismo es describe. Le caso es presentate de un patiente exhibente le principal manifestationes de convulsiones generalisate sequite per stupor. Le possibilitate de un tumor cerebral esseva eliminate. Le presentia de un allargamento diffuse del glandula thyroide con un acceptation de 51% de iodo e un conversion amontante a 83,5% in 24 horas pareva indicar le existentia de un subjacente thyrotoxicosis. Un intense tractamento antithyroide con un solution composite de iodo e Tapazol esseva instituite. Etiam Dilantina e phenobarbital esseva administrate contra le attackos convulsive. Le symptomatas se meliorava gradualmente, e le convulsiones dispareva. Le medication antithyroide esseva discontinuate durante plure menses. A iste tempore le acceptation de iodo esseva 81% e le conversion amontava a 93% in 24 horas. Per consequente le patiente recipeva 7,7 mc de iodo radioactive. Intra un mense omne le symptomatas habeva disparite. Un pregnancia subsequente non esseva sequite per un recurrentia del previe symptomatas.

Es describe altere exemplos, incluse un caso de myasthenia grave associate con toxic struma nodular e un caso de edema localisate del palpebras referibile a un hyperactive glandula thyroide.

Es sublineate le facto que un caute e meticulose scrutinio del patiente total, supplementate per pertinente studios laboratorial, pote discoperir le subjacente thyrotoxicosis in patientes qui presenta symptomatas atypic simulante morbos primari in non importa qual organo del sphaera de influentia thyroide. Le correcte regime anti-thyroide va effectuar un melioration del symptomatas o un restablimento complete.

BIBLIOGRAPHY

1. Robertson, W. E., Wohl, M. G., and Robertson, H.: Hyperthyroidism masked by symptoms of acute abdominal catastrophe, *J. A. M. A.* **108**: 623 (Feb. 20) 1937.
2. Wohl, M. G.: Metabolic disturbances simulating acute abdominal emergencies, *S. Clin. North America* **26**: 1498 (Dec.) 1946.
3. Wohl, M. G.: Masked hyperthyroidism, *M. Clin. North America* **16**: 121 (July) 1932.
4. Zondek, H.: Diseases of the endocrine glands, 4th Ed., 1944, The Williams and Wilkins Company, Baltimore.
5. Chapman, E. M., and Maloof, F.: Bizarre clinical manifestations of hyperthyroidism, *New England J. Med.* **254**: 1 (Jan. 5) 1956.
6. Scheinberg, P.: Cerebral metabolism in hyperthyroidism and myxedema, *Federation Proc.* **9**: 113 (Mar.) 1950.

ACTINOMYCOSIS: ITS RECOGNITION AND TREATMENT *

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INTRODUCTION

ALTHOUGH many of the strains of *Actinomyces* are highly sensitive in vitro to many antimicrobial agents, the disease caused in human beings by these microorganisms continues to present difficult therapeutic problems. The distinctive character of the tissue reaction offers a logical explanation for some of these problems. The involved areas are usually extensive, markedly indurated, and relatively avascular in the region of the active growth of the *Actinomyces*. These features suggest serious difficulty in getting a bactericidal concentration of the effective drug into areas of active infection, and raise serious doubts concerning the possibility of restoring the involved tissues to a nearly normal state. The two features emphasize the need for two general principles of therapy: (1) intensive and prolonged antimicrobial therapy, and (2) wide surgical excision of involved tissue.

In recent years, increasingly frequent reports of patients with actinomycotic infections are noted in the literature, suggesting either an increasing incidence and/or more effective recognition of the disease.^{1,2} During the last five years an increasing number of patients with this infection have been seen on the wards of The Johns Hopkins Hospital. In a study of these recent cases, and a review of the clinical course of other patients with this disease seen in the hospital since 1930, certain facts concerning the infection have been elicited, and, in addition, some principles for the treatment of this infection have been formulated. This communication presents these facts and principles.

OBSERVATIONS

Case Material: The records of 37 patients with actinomycosis treated in The Johns Hopkins Hospital during the last 25 years have been analyzed. In each of these cases the diagnosis was established either by culture of the organism from the site of infection, or by microscopic identification of the organism in biopsied material. Cases diagnosed clinically as actinomycosis but lacking positive confirmation by culture or biopsy have not been included. Table 1 shows the details of each case.

* Presented in part by one of us (J. C. H.) at the Thirty-seventh Annual Session of The American College of Physicians, Los Angeles, California, April 18, 1956.

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TABLE 1

J.H.H. Hist. No.	Age	Race	Sex	Occupation	Date Admitted; Complaint; Duration of Illness	Primary Site	Secondary Spread	Diagnosis Confirmed By:	Therapy	Result
1. U39197	46	W	M	Farmer	9-18-31. Swelling of jaw, 6 mos.; cough, fever, 3 mos.	Neck glands	Subcut. tissue of neck, mediastinum, lung	+ Culture	KI, incision and drainage	Death 12-1-31
2. U49534	36	N	F	Housewife	1-13-32. Pain and swelling left thigh, 10 days	Tubo-ovarian abscess, left	Psoas muscle, abd. wall. Terminally, septicemia	+ Culture	KI, incision and drainage	Death 2-10-32
3. 250097	19	W	M	Student	1-8-32. Subcutaneous abscesses left axilla, 4 yrs.	Lung abscess, LLL	Multiple chest sinuses, pleural space, retroperitoneal tissues	Biopsy	KI, incision and drainage	Lost to follow-up. Draining sinuses persisted at last exam. on 10-1-36
4. U49534	39	W	M	Merchant	5-29-33. Chronic tonsillitis, 2 yrs.	Left tonsil		Biopsy	Excision tonsils	Cured.
5. U73985	27	N	F	Cook	10-29-36. Cough and bloody sputum, 6 mos.	Lung abscess, LLL	Septicemia; multiple abscesses in heart, liver, spleen, kidneys, brain	+ Culture	KI	Death 11-18-36
6. 108720	33	W	F	Housewife	5-18-37. Left abdominal pain, 2 yrs.; wgt. loss, 1 yr.	Tubo-ovarian abscess, left	Abd. wall; septicemia; abscesses in liver, lung, nodes, long bones, brain	+ Culture	KI, incision and drainage	Death 1-1-38
7. 132739	40	N	M	Laborer	3-22-38. R.L.Q. mass, 3 mos.; draining sinus, 2 wks.	Appendix	Cecum, abd. wall, retroperitoneal tissues	+ Culture	KI, incision and drainage	Death 7-5-38
8. 158078	60	N	M	Laborer	11-21-38. R.L.Q. mass, 4 mos.	Cecum	Abd. wall, psoas muscle	Biopsy	KI, incision and drainage	Death 5-1-39
9. 178604	36	W	M	Laborer	8-10-39. Mass in jaw at site of wiring for fracture, 18 mos.	Sublingual tissues	Tissues of neck	+ Culture	KI, incision and drainage	Lost to follow-up. Draining sinus persisted at last exam. on 10-14-39
10. 197703	39	N	F	Housewife	4-9-40. Abd. pains 2 mos.; L.L.Q. mass, 1 mo.	Appendix	Cecum, abd. wall, sigmoid colon	Biopsy	KI, sulfathiazole, resection of ileum and ascending colon	Death 10-10-42

TABLE 1—(Continued)

J.H.H. Hist. No.	Age	Race	Sex	Occupation	Date Admitted; Complaint; Duration of Illness	Primary Site	Secondary Spread	Diagnosis Confirmed By	Therapy	Result
11. 203450	30	W	M	Lumbermill worker	6-19-40. Wgt. loss; abscess, left shoulder, left buttock, 4 mos.	Cecum	Abd. wall, liver, retroperitoneal tissue	+ Culture	KI, incision and drainage	Death 1-28-41
12. 113180	45	W	M	Contractor	12-9-41. Cough, 3 mos.; rt. sided pleurisy, 1 mo.	Lung abscess, RLL	Pleural space, thoracic wall, left	+ Culture	KI, closed drainage of pleura	Death 6-10-42
13. 100380	43	N	M	Laborer	1-22-41. Lumpy jaw for 24 yrs.	Tissues of neck	Multiple sinuses chest wall, osteomyelitis scapula, sacrum, left mastoiditis, lung abscess LLL, empyema, left	+ Culture	KI, sulfadiazine, incision and drainage	Death 7-1-42
14. 226413	36	W	M	Carpenter	4-9-41. Left maxillary sinusitis, orbital cellulitis, 1 mo.	Left maxillary sinus	Orbit	+ Culture	KI, sulfadiazine	Death 8-6-41
15. 207967	46	W	M	Farmer	1-8-41. Sinus tract following appendectomy 1 yr. previously	Appendix	Abd. wall, retroperitoneal tissues, subdiaphragmatic space	+ Culture	KI, sulfanilamide, incision and drainage	Lost to follow-up. Draining sinus persisted at last exam. on 2-6-42
16. 221777	59	N	F	Housewife	2-12-41. Abd. wall mass, 2 wks.	Perforation, transverse colon by fish bone	Abd. wall	+ Culture	KI, sulfanilamide, transverse colectomy	Cured. Well on last exam. on 1-10-56
17. 195826	26	W	M	Laborer	1-13-42. Abd. swelling 1 mo. after repair of perforated gastric ulcer, 2 mos. previously	Perforated gastric ulcer	Omentum, abd. wall, left thoracic wall	+ Culture	KI, incision and drainage	Lost to follow-up. Draining sinus persisted at last exam. on 2-8-43
18. 260941	24	W	M	Student	5-19-42. Abd. sinuses following appendectomy 2 yrs. previously	Appendix	Abd. wall, retroperitoneal tissues, subdiaphragmatic space, liver	Biopsy	KI, incision and drainage	Death 7-10-42
19. 267047	42	W	M	Office worker	6-30-42. Perf. ulcer, 10 mos. previously; abd. wall abscess, 1 mo.	Perforated gastric ulcer	Abd. wall, subdiaphragmatic space, liver	+ Culture	KI, sulfadiazine, incision and drainage	Lost to follow-up. Draining sinus persisted at last exam. on 3-1-43

TABLE 1—(Continued)

J.H.H. Hist. No.	Age	Race	Sex	Occupation	Date Admitted; Complaint; Duration of Illness	Primary Site	Secondary Spread	Diagnosis Confirmed By:	Therapy	Result
20. 293784	42	N	F	House maid	7-1-43. Abd. pain, 2 yrs.; weight loss L.L.Q. mass, 6 mos.	Tubo-ovarian abscess, left	Pelvic organs, abd. wall; Septicemia; abscesses in liver, spleen, lungs, and kidneys	+ Culture	KI, sulfathiazole, incision and drainage	Death 10-1-46
21. 317285	40	N	M	Laborer	3-22-44. Epigastric mass, 2 mos.	Perforation transverse colon by fish bone	Abd. wall	Biopsy	Transverse colectomy	Lost to follow-up. Well on last exam. on 5-31-44
22. 340469	39	N	M	Stevedore	9-4-45. Abd. mass and pain, 2 wks.	Perforation transverse colon by fish bone	Omentum, retroperitoneal tissues, abd. wall	Biopsy	KI, penicillin 3,000,000 U.qd. for 21 days; transverse colectomy	Cured. Well on last exam. on 3-6-56
23. 315666	19	N	M	Farmer	10-16-45. Appendectomy followed by draining sinuses, 3 yrs.	Appendix	Retroperitoneal tissues, psoas muscle, abd. wall	+ Culture	Penicillin, 100,000 U.qd. for 14 days; incision and drainage	Death 10-1-48
24. 309762	28	N	M	Laborer	4-9-46. Perforated abd. wall sinuses, 6 mos. following perforated gastric ulcer and peritonitis	Perforated gastric ulcer	Mesentery, subdiaphragmatic space, empyema, lung abscess, left	+ Culture	Penicillin, 1,000,000 U.qd. for 5 wks.; incision and drainage	Cured. Well on last exam. on 2-4-55
25. 397746	44	N	M	Laborer	8-8-46. Abd. pain; R.L.Q. mass, 1 yr.	Appendix	Cecum, abd. wall, psoas muscle	+ Culture	Penicillin, 800,000 U.qd. for 8 wks.; incision and drainage	Cured. Well on last exam. on 9-4-50
26. 407920	37	W	F	Housewife	12-18-46. Abd. sinuses; wgt. loss, 2 yrs.	Appendix	Abd. wall, psoas muscle	+ Culture	Penicillin, 1,200,000 U.qd. for 6 wks.; incision and drainage	Cured. Well on last exam. on 10-15-48
27. 361449	27	N	F	Housewife	1-20-47. Abd. sinuses following drainage pelvic abscess, 2 yrs. previously	Tubo-ovarian abscess, rt.	Abd. wall, retroperitoneal and perirectal tissues	+ Culture	Penicillin, 1,000,000 U.qd. for 1 yr.; excision infected tissue	Cured. Well on last exam. on 11-1-55
28. 478019	19	N	F	House maid	10-19-48. Draining abdominal sinuses, 1 yr.; pelvic mass, 6 mos.	Appendix	Abd. wall, pelvic organs	+ Culture	Penicillin, 1,000,000 U.qd. for 6 mos.; excision infected tissues	Cured. Well on last exam. on 7-1-50

TABLE 1—(Continued)

J.H.H. Hist. No.	Age	Race	Sex	Occupation	Date Admitted; Complaint; Duration of Illness	Primary Site	Secondary Spread	Diagnosis Confirmed By:	Therapy	Result
29. 495666	61	W	F	Housewife	3-28-49. Swollen, draining neck glands 2 yrs.	Tissues of neck	Neck tissues, ant. chest wall, left axilla	+ Culture	Penicillin, 8,000,000 U.qd. for 3 mos.; incision and drainage	Death 1-1-50
30. 146826	43	N	M	Laborer	4-7-49. Rt. flank pain, draining sinus, rt. flank, 6 yrs.	Appendix	Psoas muscle, subcutaneous tissues	+ Culture	Penicillin, 1,200,000 U.qd. for 3 wks.; incision and drainage	Cured. Well on last exam. on 1-1-51
31. 532719	66	W	F	Housewife	3-28-50. L.U.Q. pain, 10 days	Perforation transverse colon by fish bone	Abd. wall	+ Culture	Penicillin, 600,000 U.qd. for 3 wks.; transverse colectomy	Cured. Well on last exam. on 6-21-51
32. 621368	54	W	M	Painter	9-20-53. Draining sinus, left flank, 2 yrs.	Perforation recto-sigmoid	Abd. wall, retroperitoneal tissues, left kidney, cutaneous tissues of post. surface of body	+ Culture	Penicillin, 12,000,000 U.qd. for 6 mos.; excision involved tissues, left kidney, and closure of perforation in sigmoid, penicillin, 5,000,000 U.qd. for 6 mos.	Cured. Well on last exam. on 10-1-56
33. 686823	63	W	M	Undertaker	10-20-54. Headaches, chills, fever, fits, 6 mos.	Brain abscess		+ Culture	Penicillin, 12,000,000 U.qd. for 1 day; trephine evacuation	Death 10-22-54
34. 689305	45	W	M	Business executive	11-10-54. Cough, wgt. loss, 6 mos.	Lung abscess, RUL		+ Culture	Penicillin, 8,000,000 U.qd. for 6 wks.; lobectomy	Death (postop.) 12-19-54
35. 693648	49	W	M	Electric line repairman	3-7-55. Pain, rt. side of head, 6 mos.	Left middle ear	Left mastoid, left epidural abscess	+ Culture	Penicillin, 1,200,000 U.qd. for 2 mos.; excision infected tissue	Cured. Well on last exam. on 10-1-56
36. 723387	30	N	M	Farmer	12-15-55	? Perforation transverse colon	Retroperitoneal tissues	Biopsy	Penicillin, 20,000,000 U.qd. for 30 days; transverse colectomy; penicillin, 4,000,000 U.qd. for 1 yr.	Cured. Well on last exam. on 10-1-56
37. 730776	51	W	M	Paper-hanger	3-6-56. Cough, 6 mos.; wgt. loss, 1 mo.	Lung abscess, LUL		Biopsy	Penicillin, 12,000,000 U.qd. for 30 days; left lobectomy; Vicillin, 5,000,000 U.qd. for 7 mos.	Cured. Well on last exam. on 11-2-56

TABLE 2
Location of Primary Lesions

Anatomic Location	Number	% of All Lesions
Cervico-Facial Tissues	9	24
Mastoid	2	
Maxillary sinus	1	
Tonsil	2	
Neck glands	4	
Lungs	5	13
Left lower lobe	2	
Left upper lobe	1	
Right upper lobe	1	
Right lower lobe	1	
Abdominal Tissues	23	63
Perforated gastric ulcer	3	
Appendix	9	
Cecum	2	
Perforated transverse colon	4	
Recto-sigmoid perforation	1	
Tubo-ovarian abscess	4	

Thirty-one of the patients have been adequately followed for from one to 10 years. Six patients have been lost to follow-up. In this group of 37 patients there were 26 males and 11 females. Twenty of the patients were white and 17 were Negroes. The ages of the individuals varied greatly, the youngest having been 19 and the oldest 66 years of age at the

TABLE 3
Sites of Secondary Spread of Infection

Site	Number
Cervico-Facial Region	
Neck tissues	4
Mandible	3
Skull	2
Meninges	2
Brain (metastatic)	3
Thorax	
Lungs	10
Pleura	6
Thoracic wall	5
Mediastinum	1
Abdomen	
Abdominal wall	15
Mesentery	8
Retroperitoneal region	3
Colonic wall	6
Subphrenic space	4
Cecum	4
Liver	4
Gastric wall	3
Pelvic organs (female)	6

time of onset of the disease. The occupations of the individuals were quite varied. There was no seasonal factor in the onset of the disease.

Primary Lesion: The site of the primary lesion in these patients is shown in table 2. The primary infection in some of these cases occurred at the site of trauma to, or penetration of, an intact mucous membrane. Examples of this may be seen readily in table 1.

Case 9 developed infection in the cervical tissues after the buccal mucosa had been perforated by wire used to support a fractured mandible. Cases 17, 19 and 24 developed abdominal actinomycotic abscesses in association with perforated gastric ulcers. Cases 16, 21, 22 and 31 developed abdominal abscesses after swallowing fish bones which presumably perforated the colon.



FIG. 1. Cervicofacial actinomycosis. Multiple draining cutaneous sinuses in the cervical tissues and the anterior chest wall (case 29).

In cases 16, 22 and 31 the fish bone was found in the infected area at the time of operation. Case 35 suffered instrumental trauma to the left eustachian tube three months before onset of symptoms.

Secondary Lesions: Table 3 lists the sites of secondary spread of infection in this group of patients. Of the 91 different secondary lesions identified

in these 37 cases, 50 (54.9%) involved the abdominal wall or viscera, 21 (23.1%) involved the thoracic wall or viscera, and 12 (13.2%) were situated in the cervicofacial region. In only four instances was there evidence of blood stream dissemination. Examples of typical lesions are shown in figures 1, 2 and 3.



FIG. 2A. Abdominal actinomycosis. Multiple draining cutaneous sinuses over posterior surface of body and in scars of previous sites of incision of sinuses (case 32).

Diagnosis: The diagnosis was firmly established in all of these cases. Positive bacteriologic confirmation was obtained in 28 cases, while the actinomycotic organisms were identified in the biopsied material from the other nine patients. In nine of the patients from whom positive cultures were obtained, "sulfur granules" were found in the drainage from cutaneous sinuses. One patient with a lung abscess (case 34) coughed up bloody



FIG. 2B. Abdominal actinomycosis. Flat plate of the abdomen with two sinus tracts injected with iodized oil. Note that lower cutaneous sinus connects with sigmoid colon (case 32).

sputum containing large "sulfur granules." A "sulfur granule" compressed between two glass slides and stained with hematoxylin and eosin stain is shown in figure 4. A microscopic section stained with hematoxylin and eosin of biopsied material from case 3 is shown in figure 5.

Clinical Features: A fever of low grade was invariably noted unless secondary infection with other microorganisms had occurred. This com-



FIG. 3. Actinomycosis of bone. X-rays of mastoid area. Complete destruction of bony structures of left mastoid area including petrous ridge and inner table of skull outlined by arrows (case 35).

plication was observed in 20 of these patients. In such instances there was high fever of the intermittent type, swinging from 99° F. to 103° F. Each of the individuals showed a slight to moderate anemia of the normocytic, normochromic type. The sedimentation rate (Wintrobe) was elevated in each instance. There was always moderate peripheral leukocytosis. Peripheral leukocyte counts ranged from 8,000/mm³ to 14,000/mm³. Leukocyte counts over 15,000/mm³ were unusual except when there was severe secondary infection. Microorganisms cultured from the involved areas in these

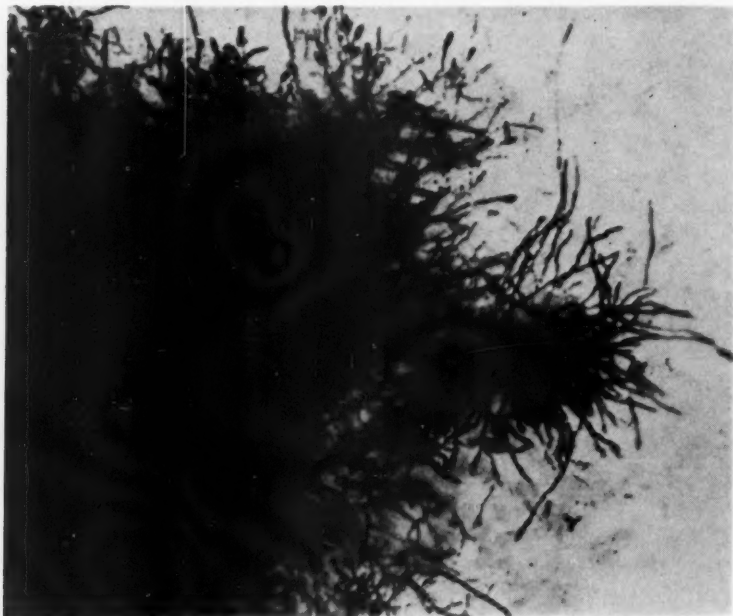


FIG. 4. "Sulfur granule." Photomicrograph of a sulfur granule compressed between glass slides and stained with hematoxylin and eosin. Typical club-shaped branched mycelia are peripheral. (350×).

secondary infections included *Staphylococcus albus*, *Streptococcus faecalis*, *Proteus vulgaris* and *Bacteroides funduliformis*.

Therapy: The treatment in this group of patients varied. Prior to 1945 no currently regarded specific treatment was given to any of these patients. Iodides were routinely administered to all patients with the disease. A few patients were treated with thymol. Irradiation of lesions was tried in a few cases. Surgical drainage of abscesses was performed occasionally. These were treated as ordinary pyogenic infections.

Since 1945 all patients have received penicillin as a specific treatment for the infection. In the earlier patients the dosage of penicillin varied from

300,000 units per day to 1,000,000 units per day. In recent years much larger doses of penicillin have been given. It is now standard practice to give 10 to 20 million units of penicillin a day, administered by the intravenous route in a continuous drip for a period of 12 hours daily.

After an initial period of 30 to 45 days of antimicrobial therapy, wide surgical excision of the infected tissues is performed. In lesions involving the superficial structures the wound is packed open and allowed to heal by secondary intention. In lesions involving the visceral structures, where this technic is obviously impossible, primary closure is effected. Eradication



FIG. 5. Biopsy of actinomycotic lesion. Colonies of actinomyces stained with hematoxylin and eosin in dense avascular scar tissue showing very little acute inflammatory response. ($\times 90$).

of the infection and healing of the wound will be satisfactory if excision has been adequate. Following surgery, 2 to 5 million units of intramuscular penicillin are administered daily for a period of 12 to 18 months. This therapy is maintained on an out-patient basis when hospitalization is no longer required. More recently (in cases 36 and 37), penicillin V (Vincillin), 5,000,000 units per day, has been given by the oral route.

Results: The results of the forms of treatment employed in these patients are presented in tables 4 and 5. Of the 31 patients adequately followed, 14 have recovered and 17 have died. Table 4 shows the effect of penicillin.

TABLE 4
Fate of Patients with Actinomycosis: Effect of Penicillin Therapy

Fate	Before 1945; Rx: KI, Thymol, Sulfa Drugs		After 1945; Rx: Penicillin	
	Number of Patients	% Total	Number of Patients	% Total
Death	13	62	4	23
Progression of illness at time of last examination; lost to follow-up	5	24	—	—
Cured	3*	14	12	77

* One patient followed for 10 years. The second patient was well at last examination, two months after discharge, but was lost to subsequent follow-up. A third patient had infection in the crypts of tonsils, found incidentally at tonsillectomy.

Table 5 shows the effect of surgical excision of infected tissues alone and the effect of combined surgical excision and penicillin therapy.

COMMENT

Historical: Bollinger³ in 1877 reported that he found branching mycelia in the material discharged from a diseased mandible of a cow. He considered these to be the cause of the suppuration and bony destruction. Harz⁴ studied this organism given him by Bollinger and named it "strahlenpilz" (ray-fungus), or Actinomyces, from its microscopic appearance. In 1878 Israel⁵ found the organism in human autopsy material, and in 1879 Ponfick⁶ first recognized the condition during life. Israel⁷ in 1885 reported in detail

TABLE 5
Cure Rate in Actinomycotic Infections: Effects of Types and Combinations of Treatment

Type of Treatment	Number of Cases	Number Cured	% of Total Number Patients in Treatment Category
General supportive measures only; no specific treatment	17	0	0.0
Excision of infected tissues	4	2	50.0
Penicillin therapy only	7	4	57.1
Excision of infected tissues plus penicillin therapy	9	8	88.8

38 cases of the disease in human beings, and to him goes the credit for clearly defining the clinical entity. Since that time innumerable articles have been written about the disease, as well as several monographs, among which is the excellent study by Cope.⁸

Bacteriology: The causative agent of this disease is a gram-positive, branching filamentous microorganism, related more to the true bacteria than to the fungi with which it is often classed. It is strictly anaerobic in growth.

Isolation is best carried out in Brewer's thioglycollate medium or on plates of blood agar under anaerobic conditions. Wolff and Israel⁹ published the first good bacteriologic studies on the organism in 1891, followed by Wright¹⁰ in 1905. The organism was called *Actinomyces bovis* (Wolff-Israel) by Wright. Since then it has also come to be called *Actinomyces israeli*.

Pathogenesis: Israel believed but did not prove that the disease was endogenous in origin. He pointed out that the causative organism was an anaerobic one which could not be isolated from the environment. Others at that time, notably Bostroem,¹¹ held that the human infection was exogenous and closely related to the bovine infection. Bostroem laid stress upon contact with infected animals, either directly or indirectly through the medium of contaminated vegetable fomites. The apparent increased incidence of disease in the rural population or in individuals who had the habit of chewing on straw, hay or grass, as well as the apparent seasonal incidence of the disease, was cited to support his concept.

It is now clear that this concept is incorrect, though it dies hard. The many large reported series of cases of actinomycosis have failed to substantiate any occupational predilection or seasonal variation in onset. In the series of cases reported here there is no correlation with age, race, sex or occupation. Likewise there appears to be no seasonal factor in the onset of the disease.

Israel reported among his original group a case of pulmonary involvement which developed after aspiration of a tooth. At autopsy the center of infection was found to contain fragments of tooth. He noted, too, the frequent association of trauma as a predisposing factor in the development of the disease. He pointed out the association of diverticula in the colon with abdominal actinomycosis. In considering the pathogenesis, Israel wrote in 1885 that actinomycosis "... cannot infect the body without first having penetrated the body through the mucous membrane of the respiratory or alimentary tract, or through the external skin."

In 1910 Lord¹² noted the association of actinomycotic infections with dental caries. He was able to culture the organism from dental cavities and from tartar scraped from teeth. Other investigators^{13, 14} have confirmed this finding. Lord¹² also isolated organisms from the crypts of the tonsils. Kaye¹⁵ was able to isolate and culture *A. israeli* from bronchoscopic aspirations of 65 of 240 consecutive patients. The organisms have been cultured from the stomach and vaginal mucosa of animals.³

It is now clear that Israel's concept of the endogenous origin of infection is correct. The organisms, which normally inhabit the mucous membranes, gain entrance to deeper tissues through a break in the mucous membrane. Cases have been reported occurring after dental extraction,¹⁶ penetration by foreign bodies through tonsillar tissue,¹⁷ aspiration of teeth,¹⁸ rupture of gastric or duodenal ulcers,¹⁸ rupture of the appendix,¹⁹ rupture of diverti-

cula of the colon,⁷ and perforation of rectal abscesses.²⁰ Ascending actinomycotic infection involving the ureter, renal pelvis and renal cortex has been reported in a case of ureteral transplantation to the colon.²¹

The association of perforation of the alimentary tract and actinomycotic infection within the abdomen is seen in the cases reported in this communication. Abdominal involvement was noted after rupture of gastric ulcers and after perforation of the colon by fish bones. In three instances at operation the fish bones were recovered from the abscesses.

Distribution of Lesions: The anatomic distribution of primary lesions in the patients reported in this communication is at variance with that generally reported for actinomycotic lesions. The quoted incidence of cervicofacial lesions is about 63%, of abdominal lesions about 22%, and of thoracic lesions 15%.⁸ In the present series the abdominal lesions comprised 63% of the total, cervicofacial lesions 24%, and thoracic lesions only 13%.

This difference in the distribution of the primary site might well be explained by more accurate diagnosis. An increased awareness of the disease on the part of the house physicians in this hospital has effected an intensive and diligent search for "sulfur granules" in all patients with draining sinuses. Better cultural technics are now routinely employed in the bacteriologic laboratory. The routine use of Brewer's thioglycollate medium has increased the detection of anaerobic organisms. Also, more patients suffering from illnesses diagnosed clinically as pulmonary or abdominal tuberculosis or malignancy are now currently being subjected to surgery for either diagnostic biopsy or definitive surgical procedures. Many of the patients in this series who were found to have thoracic or abdominal actinomycosis were initially diagnosed as tumor or tuberculosis. It was only at operation, when an unexpected tissue reaction not resembling malignant or tuberculous tissue was found and biopsied, that actinomycotic infection was proved. This has been the experience of others who have recently reported on actinomycotic infections.^{1, 2} Cope reported that, of six patients with abdominal actinomycosis, five were originally operated on because they were thought to have a malignant lesion. Only at operation was the peculiar tissue reaction noted which on microscopic study showed lesions of actinomycosis.²⁰

Pathologic Findings: The involved tissues in actinomycotic infection are markedly indurated and relatively avascular. The lesions are subacute or chronic and progressive in character. The involved tissues become hard and swollen, but have little tendency to early suppuration. They do have a tendency to form multiple draining fistulae. The lesions spread extensively to adjacent structures and organs. Large areas of subcutaneous tissue and muscle, as well as lymph nodes, mesentery, bone or viscera, may frequently be involved. The only tissue which consistently escapes is surface epithelium.

At some time necrosis does occur and abscess formation results. Within these abscesses the conglomerations of organisms (the "sulfur granules")

can easily be seen. These may be discharged intermittently through the cutaneous sinuses. The identification of "sulfur granules" in the drainage from the fistulae makes the diagnosis certain. If this disease is suspected, the gauze dressings should be examined each time they are changed. Diligence and patience are almost invariably rewarded by positive results.

Therapy: The treatment for this infection has been varied. Surgery, chemotherapy, irradiation and vaccines have all been used, singly and in combination. When potassium iodide was used empirically by Thomassen²² in 1885 for the treatment of actinomycosis of the tongue in cattle, he was quite unaware that this granulomatous process was caused by an *Actinobacillus* (an aerobic gram-negative bacillus which is specifically destroyed by potassium iodide), rather than by *A. israeli* (an anaerobic gram-positive branched organism which may grow in vitro in media containing potassium iodide). He popularized this form of therapy, an error which has been perpetuated to the present time. Thymol, copper sulfate and other chemotherapeutic agents were in vogue at one time or another, as was vaccine therapy. None was specific. Waring¹⁹ first introduced surgery as a definitive form of therapy. He emphasized incision and drainage of abscesses. Wangenstein²³ emphasized the importance of surgical excision of the dead tissue as the most direct attack upon the disease.

It is obvious from the type of tissue reaction that any chemotherapeutic agent used in the treatment must be administered in large amounts to get an effective level into the relatively avascular area. When sulfonamides and penicillin were introduced they were found to be effective in inhibiting the growth of the organism in vitro. Fisher²⁴ reported in 1943 that a strain of *A. israeli* isolated from a patient (case 20) was extremely sensitive to crude penicillin. Herrell²⁵ was the first to use penicillin in the treatment of patients with actinomycosis. He reported that, of three patients with cervicofacial disease, two responded well to the administration of penicillin of 40,000 units per day by intravenous drip for a period of two weeks. Later Dobson and Cutting²⁶ reported success in treating three patients with actinomycosis. Two of these were of the cervicofacial type, and in one the lung was involved. They were treated for one week with penicillin, 1,000,000 units per day by intravenous drip, followed by 120,000 units per day in divided doses by the intramuscular route for one month. The follow-up period was six months.

Considering the tissue reaction caused by infection with *A. israeli*, the authors in 1952 felt that wide surgical excision should be employed in conjunction with the administration of massive doses of penicillin systemically. Since that time the patients who have been seen on the wards of The Johns Hopkins Hospital have been given this treatment, a combination of initial massive penicillin therapy, wide surgical excision of infected tissue, and long-continued penicillin therapy in a dosage of 2 to 5 million units per day for 12 to 18 months after excision. With the use of this treatment in nine

cases the cure rate has been raised to 88%, with a follow-up period of from six months to three years. The one death (case 34) which occurred in the group treated with massive doses of penicillin and subjected to surgery must statistically be considered a failure of this form of therapy. It should be noted, however, that death was caused by uncontrollable bleeding due to the development of thrombocytopenia subsequent to multiple blood transfusions.

CONCLUSIONS

1. The preferred treatment of this disease is a combination of massive, long-term administration of penicillin and wide surgical excision of infected tissues. With this combined therapy the cure rate in this infection has been raised to 88% at The Johns Hopkins Hospital during the last five years.
2. The anatomic location of the primary site of infection in this series is at variance with that commonly reported. In this series, 63% of the primary lesions are in the abdominal region, whereas only 24% are in the cervicofacial region.
3. The concept of endogenous origin of the infection is supported by the material presented in this series of cases.

SUMMARY IN INTERLINGUA

Racias de *Actinomyces* es sensibilissime a agentes antimicrobial in vitro, sed le morbo que es causate in humanos per iste micro-organismos continua presentar difficile problemas therapeutic. Proque le historeactiones es extense, indurate, e relativamente avascular, le passage de concentrationes bactericida de un droga efficace usque a intra le area del infection non es facile a effectuar. Duo principios therapeutic general es (1) le requirimento de intense e prolongate therapia antimicrobial e (2) le indication de extense excisiones chirurgic del tessuto afficte. Es presentate un revista del protocollas de 37 patientes con actinomycosis tractate al Hospital Johns Hopkins. Le distribution del lesiones es multo differente ab illo communmente acceptate. In le serie hic presentate, lesiones abdominal representa 63 pro cento del total, lesiones cervicofacial 24 pro cento, e lesiones thoracic 13 pro cento. Es exprime le opinion que le differentia del distribution se explica per un plus accurate diagnose. Le pathogenese de iste infection es endogene. In multe casos il habeva definite indicios de perforation de un normal membrana mucose. Le therapia non succedeva troppo ben usque al introduction de un programma combinate de massive e prolongate administrationes de penicillina e extense excisiones chirurgic del tessuto interessate. Iste plano ha essite usate in nove casos. A iste hospital illo ha resultate in un melioration del proportion de curationes usque a 88 pro cento, con observationes consecutori durante periodos de inter sex menses e tres annos.

BIBLIOGRAPHY

1. Sanford, G. E., and Barnes, R. O.: Massive penicillin therapy of abdominal actinomycosis, *Surgery* 25: 711, 1949.
2. McVay, L. V., and Sprunt, D.: A long-term evaluation of Aureomycin in the treatment of actinomycosis, *Ann. Int. Med.* 38: 955, 1953.
3. Bollinger, O.: Ueber eine neue Pilzkrankheit beim Rinde, *Centralbl. f. d. med. Wissensch.* 15: 481, 1877.

4. Harz, C. O.: *Actinomyces bovis*, ein neuer Schimmel in den Geweben des Rindes, Jahresbuch d. konigl. Central-Thierarzneischule zu München, 1877, p. 125.
5. Israel, J.: Neue Beobachtungen auf dem Gebiete der Mykosen des Menschen, Arch. f. path. Anat. Berlin **74**: 15, 1878.
6. Ponfick, E.: Ein Vortrag über Actinomykose des Menschen, Breslau Aerztliche Zeitschrift **2**: 151, 1880.
7. Israel, J.: Klinische Beiträge zur Kenntnis d. Aktinomykose des Menschen, 1885, Hirschwald, Berlin.
8. Cope, V. Z.: *Actinomycosis*, 1938, Oxford University Press, London.
9. Wolff, M., and Israel, J.: Über Reincultur des Aktinomyces und seine Übertragbarkeit auf Thiere, Arch. f. path. Anat. Berlin **126**: 11, 1891.
10. Wright, J. H.: The biology of the micro-organisms of actinomycosis, J. Med. Research **13**: 349, 1905.
11. Bostroem, E.: Untersuchungen über die Aktinomykose des Menschen, Beitr. z. path. Anat. u. z. allg. Path. **9**: 1, 1891.
12. Lord, F. T.: The etiology of actinomycosis: the presence of *Actinomyces* in the contents of carious teeth and the tonsillar crypts of patients without actinomycosis, J. A. M. A. **55**: 1261, 1910.
13. Rosebury, T., Epps, L. L., and Clark, A. R.: Study of isolation, cultivation, and pathogenicity of *Actinomyces israeli* recovered from human mouths and from actinomycosis in man, J. Infect. Dis. **74**: 131, 1944.
14. Onisi, M., and Nuccolls, J.: *Actinomyces* and other pleomorphic organisms recovered from pigmented carious lesions of human teeth, Oral Surg., Oral Med. and Oral Path. **7**: 629, 1954.
15. Kaye, E. B.: Pulmonary actinomycosis, its treatment by pulmonary resection in conjunction with chemotherapy: report of two cases, Ann. Surg. **124**: 535, 1946.
16. Axhausen, G.: Das Frubild der Tieferaktinomykose, Deutsch. med. Wchnschr. **62**: 1449, 1936.
17. Klinefelter, H. F., and Humphries, W. C.: Cervical actinomycosis with imbedded foreign body and without sinus formation, Ann. Int. Med. **27**: 638, 1947.
18. Cope, V. Z.: Visceral actinomycosis, Ann. Roy. Coll. Surgeons England **5**: 394, 1949.
19. Waring, H. J.: Actinomycosis of the cecum, vermiform appendix and right iliac fossa, St. Bartholomew's Hosp. Rep. **41**: 197, 1905.
20. Cope, V. Z.: Actinomycosis involving the colon and rectum, J. Internat. Coll. Surgeons **12**: 401, 1949.
21. LeBrun, H., and Gilmour, J. E. W.: Hypokaloemia and renal actinomycosis following ureterocaecostomy: report of a case, Brit. J. Urol. **25**: 133, 1953.
22. Thomassen, H. J. P.: L'Actinomycose, L'Echo Vet. **15**: 409, 1885.
23. Wangenstein, O. H.: The role of surgery in the treatment of actinomycosis, Ann. Surg. **104**: 752, 1936.
24. Fisher, A. M.: The anti-bacterial properties of crude penicillin, Bull. Johns Hopkins Hosp. **73**: 343, 1943.
25. Herrell, W. E.: The clinical use of penicillin, J. A. M. A. **124**: 622, 1944.
26. Dobson, L., and Cutting, W. C.: Penicillin and sulfonamides in the therapy of actinomycosis: report of 16 additional cases and in vitro tests of susceptibility of actinomyces to penicillin and sulfadiazine, J. A. M. A. **128**: 856, 1945.

THE EFFECT OF THE PHYSICIAN'S "PSYCHE" UPON THE PATIENT'S "SOMA" *

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THE modern period of investigative psychosomatic medicine might be considered to have been initiated by Walter Cannon's studies on the physiology of rage and fear, and to have culminated in the detailed correlative studies of the rôle of emotions upon disease states. The impact of this large body of work has led to the widely taught and well accepted axiom that the patient's feelings, moods and attitudes may significantly influence the course of a given disorder. Less attention, however, has been accorded to the effect upon the course of an illness of the physician's attitudes and feelings toward the patient. This facet of psychosomatic medicine probably has not been emphasized because the physician's rôle is usually considered to be that of an objective and rational observer, tempered by a perceptive attitude of warmth and sympathy. That so ideal a picture is not the case is well recognized by most physicians; what factors are responsible for the departure from the ideal are, however, rarely explored or reported.

During the last eight years in the Department of Medicine at Duke Hospital a 10-month program of exploratory psychoanalytic interviews has been made available to the Chief Resident. This has afforded an opportunity for the internist to review critically his personal relations with patients and colleagues, and to provide a structured basis for evaluating the importance of these relationships in the care of the patients. The following case reports are designed to illustrate how such an experience may be made to bear upon house staff and student training. One of the major propositions of this presentation is that the attitude of the physician towards the patient and his illness may very well influence the course of the illness, and that often these attitudes and feelings are rooted in experiences not immediately pertinent to the clinical problem under study.

CASE REPORTS

Case 1. A 48 year old white male physician had been followed for four years for an extraordinarily complicated illness. He was a "brittle" diabetic who had developed pulmonary tuberculosis four years prior to the present admission. A thoracoplasty was performed two years later, the postoperative period being complicated by the development of acute pancreatitis with residual chronic pancreatic insufficiency, a localized empyema with pleurocutaneous fistula formation, and an episode of homologous serum hepatitis. Three weeks prior to the present admission he had

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developed generalized anasarca, and preliminary evaluation indicated the clinical and chemical characteristics of the nephrotic syndrome. The underlying cause for the syndrome was unknown, but amyloid disease was suspected.

On admission to the hospital the patient was a pale, thin individual with marked sacral and lower extremity edema, a draining sinus in the right chest, and a palpable right kidney. Having been in the hospital on many previous occasions he was well known to the staff. He was considered by them to be a difficult patient to manage: he was said to be constantly complaining about inadequacy of meal service, nursing care, and attention of the interns to his draining sinus. Whenever a change in medication was to be instituted, long and repeated explanations were necessary. He was often heard to disparage one physician to another.

Not long after his admission the attending intern and resident were "fed up," and they began to make very quick order of their daily rounds upon the patient. The tone of hostility of the house staff became quite general and easily recognized whenever the patient's case came up for discussion. It was pointed out at this juncture that the patient's ability to generate antagonism might be looked upon as another specific facet of this man's illness, requiring therapy as much as his other difficulties. An attempt was made during this consultation with the house staff to indicate that to "get mad at the patient" was to only further complicate his care.

Two weeks later a review of the patient's status revealed a sustained fever of three days' duration. In further conference with the house staff it was learned that the febrile illness had not been thoroughly studied (no recent complete physical examination, no extensive bacteriologic studies). The attitude of the staff was again underscored, as was the fact that their feelings of antagonism had probably led to infrequent visits and checks. They readily admitted that morning rounds consisted of merely walking in and out of his room in attempt to escape his diatribes.

Within the next day adequate studies were conducted and a urinary tract infection was disclosed. Appropriate antimicrobial therapy was begun. Final consultation with the staff indicated that such a vociferously complaining patient often made them feel uneasy and doubtful. It was emphasized that it is most important that such feelings be recognized, since the management of this patient's infectious disease, primarily its duration, might be considered to have been directly influenced by their feelings toward the patient. The staff was willing to grant this premise, but they remained firm in their attitude that the patient was overly demanding.

Comment: This case demonstrates the effect of feelings of hostility upon the part of the physician towards the patient, and illustrates the pernicious quality such feelings may have upon the medical management of the individual. In this instance, hostility led to errors of omission. Though there is little that can be done to alter the immediate reaction of the physician to a difficult patient, it is most important that the physician constantly be self-critical in assaying his feelings of hostility, and consciously guard against their influencing his conduct of the clinical problem. This type of self-appraisal is almost always necessary, but is of utmost importance in situations where antagonisms are experienced. It is among house officers and other physicians in the early stages of training that the pitfalls of hostile attitudes are most likely to be experienced. We believe that training at this level should include specific concern with these problems.

Case 2. A 40 year old Negro male entered with the chief complaint of periodic episodes of headache for the last five years. They were characterized by the de-

velopment of a series of high intensity headaches, usually in the early fall and spring of the year, most often unilateral in location, pulsatile in quality, and of a degree severe enough to warrant his stopping work. The headache "clusters" would persist for from 10 to 21 days and then gradually recede. During this two- to three-week period the patient did little or no work. He was employed as a dishwasher in a hospital kitchen, and previously had worked as a kitchen employee in a restaurant.

On physical examination the patient was a well developed individual in moderate distress, complaining of headache. Pulse, temperature and blood pressure were all unremarkable. Neurologic examination was within normal limits. The admitting diagnosis was migraine headaches of the Horton "cluster" variety.

In consultation with the house staff regarding this patient, the question was raised as to the possibility of any underlying personality problem that might be acting as a trigger mechanism for the headache episodes. The generally held opinion of the house staff was, "The patient doesn't have many problems . . . how could he? He's just a dishwasher, has been a kitchen worker all the time." It was further emphasized by the house officer that a Negro individual of the patient's economic and social level "rarely has the problems we usually think play a rôle in migraine." At no time in discussing this facet of the patient's illness was the house officer disparaging in his tone or content. He merely felt that in such an individual the more complex and structured problems that have been associated with migraine headaches could not obtain.

A series of interviews with the patient was then conducted. It was quickly learned that the patient held several interests beyond his work, many of an intellectual caliber. He was very active in local Negro affairs, being particularly concerned with the problems of integration. He worked part-time on the Negro newspaper, was chairman of several committees of the Negro chamber of commerce, and had many times led campaigns in church groups to increase community participation in furthering integration. While in the hospital the patient experienced a temporary remission of the headaches, which, however, appeared to be reactivated following an important address by the governor of the state in which the governor forcefully denounced integration. The day following this well publicized speech the patient experienced a severe migraine attack. During the remainder of the hospitalization further exploration of the patient's attitudes concerning his rôle as a Negro was conducted, and upon his discharge from the hospital several similar interviews were carried out on an out-patient basis. The patient remained headache-free for the ensuing 10 months of follow-up.

The content of the interviews was made known to the house officer, who was quite surprised by the patient's interests and demonstrated abilities regarding community activities. It was emphasized to the house physician that his attitude towards this patient was probably predicated by patterns long since established and not necessarily pertinent to the specific case in point; further, that similar prejudice in other clinical problems should be carefully guarded against, since the ability to conduct effective therapy could well be circumscribed by such prejudice.

Comment: This case demonstrates the limitations that may be placed upon clinical acumen by attitudes and feelings learned many years previously. The house officer's consideration of the patient's intellectual abilities, though by no means hostile or disparaging, was circumscribed by his previous background in which a degree of activity and feeling such as that demonstrated by the patient was not ascribed to unskilled Negro workers. Since the ultimate management of the patient's illness required a consideration of the problems that the patient might have been experiencing in his daily life, it

was important that the house officer be able to explore these areas. Not until the influence of his (the physician's) past teachings—the attitudes towards Negroes expressed in his home, school, town, etc.—was discussed and demonstrated to limit his rôle as therapist in the clinical problem did the house officer appreciate the need for being aware of these facets in the management of patients. Once these attitudes of old vintage had been explored the physician was better able to manage the patient.

Case 3. A 38 year white male was admitted for treatment of recurrent pulmonary emboli with infarction. The illness had begun three years previously with the incipient development of an episode of acute bilateral thrombophlebitis. During this three year period the patient had been hospitalized several times and had been on almost constant anticoagulant therapy, the course of which had been marked by some minor periods of excessive bruising and by one episode of hematuria of sufficient degree to warrant emergency hospitalization.

During the most recent admission preceding the present stay in the hospital the patient had been noted to be "difficult to manage." There had been an occasional heated exchange between the patient and the nurses regarding proper Dicumarol dosage, and the patient was reported to have complained excessively to the house staff. His prothrombin time varied strikingly, and he required three weeks of hospital observation before a stable level was attained. He was discharged to go home during the Christmas holidays, instructed regarding Dicumarol dosage, and advised either to return to the Durham hospital for prothrombin time measurements or to have such determinations run at his local hospital. The patient returned one week later complaining of left chest pain and shortness of breath, and stating that "I have had another embolus."

The history revealed that during the week out of the hospital he had failed to take his Dicumarol and had not had the local hospital run the prothrombin time. The admitting physician chastised the patient severely for these breaches of co-operation, and indicated to the patient and to the other house officers on the ward that the patient was most unreliable. He recommended that anticoagulation be abandoned and that inferior vena cava ligation be carried out. This latter suggestion was supported by the attending physician, who saw the patient briefly on rounds, the case being presented by the admitting house officer.

During an interview with the patient at a student-attended conference designed to learn why the patient was so difficult to handle, the patient related the details of the import of his illness to him:

He had lost his job and had been advised by his private physician to stay at modified bed-rest for six months, during which time he was subjected to ridicule by neighbors and family, who found him "looking well" and could not understand why he was unable to return to work. During this period of confinement he had read at some length about his disease and understood that he could withstand "just so many plugged up blood vessels in my lung," and he was most wary of the bleeding complications of Dicumarol, since he had overheard several physicians comment on the threat of renal failure during his hospitalization for hematuria. Furthermore, he related that his private physician at home had expressed disagreement with the plan of the Durham hospital staff that anticoagulation be used. More often than not, the patient decided the proper dosage. He related that during his preceding hospitalization he had wanted to talk about these things but no one seemed particularly interested. He admitted he had been "difficult. . . . I thought maybe they would pay me some heed. . . . I was quite wrong."

When this aspect of the problem was brought to the attention of the house staff

the tone of the care was markedly altered, and an attitude of sympathy was expressed. With this change in viewpoint toward the patient there developed an interest in avoiding so conclusive a procedure as vena cava ligation, and a continuation of anticoagulant therapy was embarked upon rather enthusiastically. After several more interviews the patient reported that he thought he "ought to get along a lot better now and be able to get back to work."

Of further interest in this case was the fact that several consultants had seen him regarding the type of therapy to be used. Those consultants who were presented the case by the house staff voted for vena cava ligation; those who examined the patient independently and were unaware of the patient's relationship with the house officers supported anticoagulant therapy.

Comment: This case illustrates again the effect of hostility on the part of the physician upon the management of a clinical problem. In this instance the feelings of aggression were influencing the type of care to be outlined. When the cross-currents were detected and afforded adequate expression, a proper judgment regarding therapy was allowed. When "difficult" patients are encountered it is crucial that the basis for patient reluctance be purposely explored, and that the reaction of hostility that the physician might first experience be recognized and resolved. Alertness to this reaction of hostility and its rational resolution will permit continued objective management.

Case 4. A 40 year white male was admitted for management of the malignant phase of essential hypertension which he had had for 12 years. The patient's major complaints were headaches, blurred vision with recent development of a blind area in the left eye, and marked easy fatigability. On physical examination he demonstrated a blood pressure of 250/160 mm. of Hg, grade IV fundus changes, a loud aortic second sound, and slightly thickened peripheral blood vessels. He was placed on bed-rest, the rice diet and hypotensive drugs. During the next week the level of the blood pressure was gradually reduced. The patient, however, began to note postprandial nausea and vomiting. He ascribed this to the rice diet, and very vigorously asserted to the resident physician, "I'd rather be dead than eat that diet. You don't know what you're doing to me. I'll sign out rather than take rice." The diet was immediately discontinued.

When the senior attending physician reviewed the problem he was apprised of this change in management. He offered the opinion that failure to insist upon the use of the rice diet was a compromise that might prove unfortunate; in his judgment, the rice diet was most necessary to effect recovery from malignant hypertension. The house officer replied that he agreed with this position, and that he had seen several patients with severe hypertension do extremely well on the diet, but that he did not know how to pacify the patient. It was then pointed out to him that the patient's reaction to the diet might represent some other, more obscure problems, and that an attempt to get at these attitudes might lead to an answer. The house officer readily admitted that when the patient violently objected he had not wanted to antagonize him further by insisting on the diet, and that, since the episode, he had spent very little time with the patient.

In the ensuing days interviews were conducted with the patient that touched on many of his personal problems, and a close, sustained relationship was established. While these interviews were being conducted the patient readily returned to the rice diet and experienced no nausea or vomiting. The house officer now stated that he felt more secure with the patient: "I think we can take care of him much more easily."

Comment: This case illustrates the effect of a patient's threatening the security of the physician's rôle and forcing him to consider the possibility of rejection. In an attempt to avoid this outcome the physician maintained his security by compromising the plan of treatment. By recognizing the importance of having the patient accept him as physician and appreciating that the patient was challenging this rôle, the house officer might better have been able to direct the institution of an unpleasant remedy. It is important that the physician be aware of patient rejection or challenge, and that he realize that the feelings aroused by such an experience can often influence his plan of management.

SUMMARY AND CONCLUSIONS

The area of psychosomatic medicine has classically been considered to embrace that facet of internal medicine which is concerned with the effects of the patient's feelings and attitudes upon the course of the illness. Among internists the importance of the attitudes of the physician toward the patient and his illness has received less emphasis. We have presented four case histories which we believe illustrate the effect of the physician's attitude upon the course of illness. Two of the case presentations (cases 1 and 3) demonstrate the effect of feelings of hostility on the part of the physician. We would like to emphasize that these feelings can be most pernicious in altering the management of a clinical problem and influencing objective judgment. Case 2 illustrates that a physician's background, particularly the social evaluations learned in that background, can limit the extent of the rôle of therapist, and suggests that the prejudgments that might arise out of such experience be looked for and recognized as possible limiting factors. Finally, case 4 demonstrates that the physician must be aware of the importance of patient acceptance in his work, and that when security of his role is threatened or rejected, his course of action must not be misdirected by his attempts to protect that role. The physician must be constantly willing to undergo self-criticism and appraisal, and thereby be able to recognize the feelings and attitudes that may pertain not to the clinical problem but to his own relationship to the patient. This facet of caring for sick people should be emphasized in the training of students and house staff, since it is at the very threshold of clinical experience that the feelings of the physician might intrude unsuspectingly upon the clinical problem.

ACKNOWLEDGMENTS

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SUMMARIO IN INTERLINGUA

Le medicina psychosomatic se ha occupate primarimente con considerationes del effecto del attitudes e statos emotional del patiente super le genese e le historia natural de varie disordines. Le rolo del attitudes e emotiones del medico in lor influencia super

le morbo del patiente non ha recipite multe attention. Durante le passate octo annos le Medico-Chef-in-Residentia del Departamento de Medicina al Hospital Duke ha habite le possibilitate de servir se de un programma de interviews psychoanalytic de un duration de 10 menses. Iste programma ha fornite le base pro un revista del parte que le emotiones del medico ha in determinar le curso del morbo de un patiente individual.

Le revista ha rendite evidente que le attitudes del medico pote afficer le modos del morbo de maniera significative e que illos pote determinar a un certe grado le successo o non-successo del regime therapeutic. Es citate studios de casos que demonstra (1) le effecto del hostilitate del medico super le establimento del correcte diagnose, (2) le effecto de "previamente apprendite comportamentos social" super le correcte evaluation de un problema clinic, e (3) le effecto de attitudes de auto-protection del parte del medico super le successo del tractamento de un patiente "difficile."

Iste aspecto del medicina psychosomatic es sublineate in le programma de education pro studentes e membros del personal hospitalari, proque il es al prime initio del experientia clinic que le emotiones e attitudes del medico pote immiscer se inconsciente in le problema clinic.

COMBINED HYPERSENSITIVITY REACTION TO SODIUM PARA-AMINOSALICYLATE AND ASSOCIATED ANTIBACTERIAL DRUG CONCURRENTLY ADMINISTERED *

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IN the present-day management of tuberculosis, treatment with various combinations of streptomycin, isoniazid and para-aminosalicylic acid salts,[†] is standard practice. As is well known, each of these drugs may produce hypersensitivity reactions. It is not well known, however, that an allergic response may occur during treatment with a combination of two of these agents which is triggered by both. Two such unusual cases occurred recently at this institution, manifesting a peculiar reaction previously attributed to PAS alone. A third case presented the same uncommon response while on combined therapy, but was subsequently considered to be sensitive only to PAS.

A survey of the literature reveals few cases similar to these. Because of the interesting nature of the episodes, and the interesting possibilities concerning the mechanisms involved, we feel the problem deserves re-emphasis.

CASE REPORTS

Case 1. The patient, a 32 year old white male physician, had been known to have a 1 cm. nodule in the periphery of the right lung in the first interspace for two years. A chest roentgenogram in July, 1955, showed it to have a radiolucent center.

The pertinent laboratory findings on admission were: red blood cells, 5,000,000; white blood cells, 6,000; neutrophils, 50%; lymphocytes, 46%; eosinophils, 3%; basophils, 1%; hemoglobin, 15.9 gm.%; sedimentation rate, 7 mm./hr. The sputum was repeatedly negative on both smear and culture for acid-fast bacilli. It was decided, nevertheless, to treat the patient for pulmonary tuberculosis.

Course in Hospital: Medication with INH, 100 mg. three times a day, and PAS, 4 gm. three times a day, was instituted on September 21, 1955. The patient had no difficulty until the twenty-sixth hospital day, at which time he began to notice pains in the legs and cervical region, and chills and fever. The following day he had a severe chill and the temperature rose to 103.2° F. (figure 1). Physical examination at this time showed slight redness of the throat, enlarged cervical, axillary and inguinal lymph nodes, a faint scarlatiniform rash over the thorax, and palpable liver and spleen. There was a relative lymphocytosis, and atypical lymphocytes were

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[†]The following abbreviations will be used in this paper for simplicity of expression: PAS for the sodium or potassium salt of para-aminosalicylic acid; SM for streptomycin; INH for isoniazid (iso-nicotinic acid hydrazide).

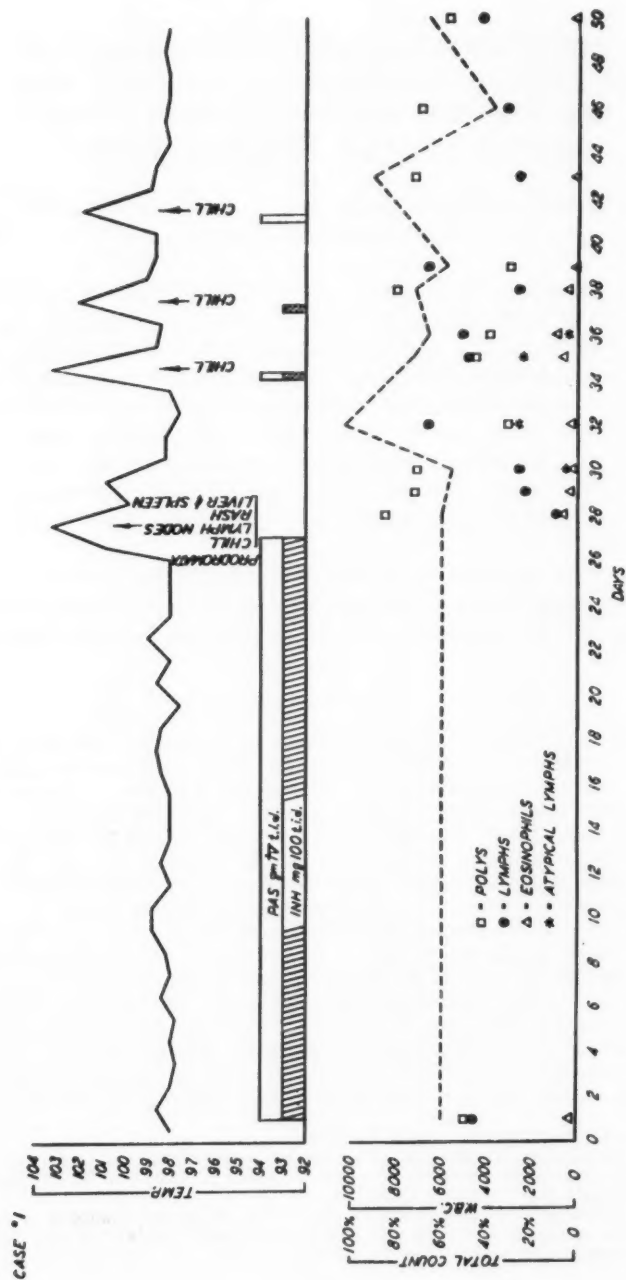


FIG. 1. The relationship between the medications, temperature and white blood count in case 1.

CASE #2

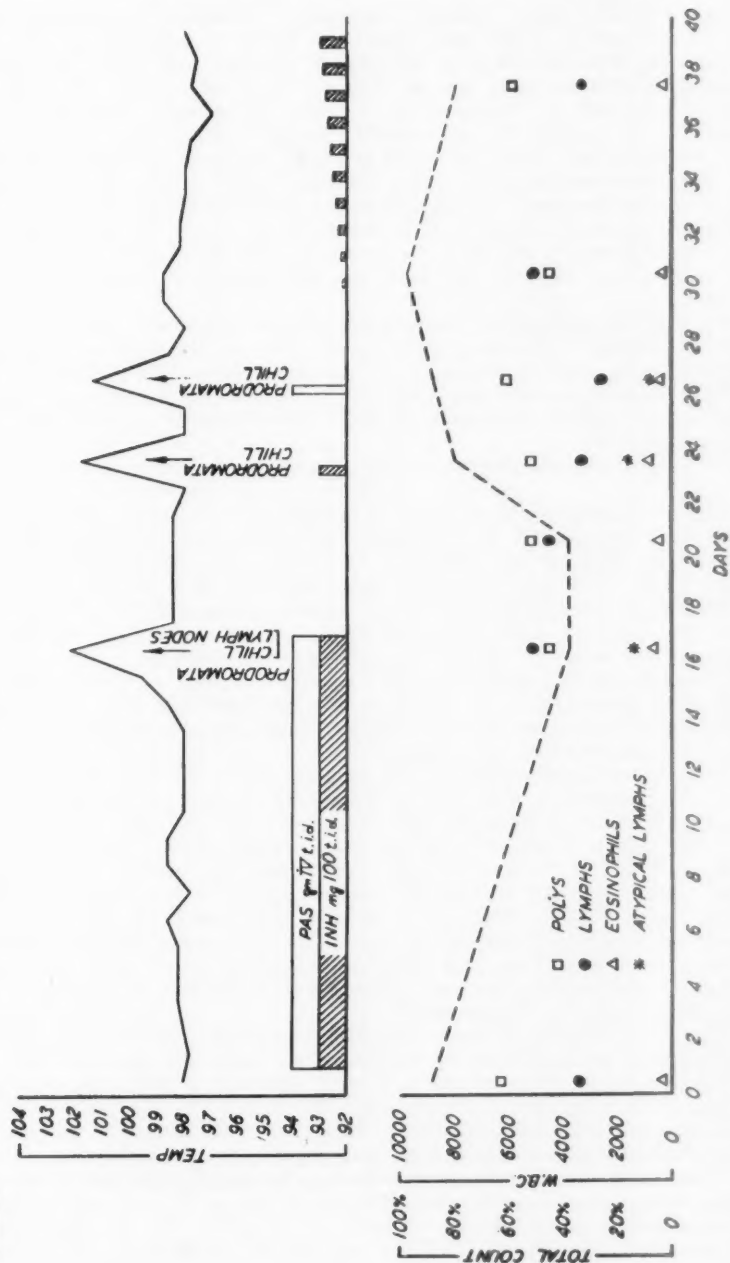


FIG. 2. The relationship between the medications, temperature and white blood count in case 2.

seen in the blood smears. Although a diagnosis of infectious mononucleosis was suspected, all medication was discontinued and within 24 hours the patient was asymptomatic. After one week he received 100 mg. INH and 4 gm. PAS simultaneously. Within two hours this was followed by a shaking chill and a rise in temperature to 104° F. Because PAS has been incriminated previously in the etiology of an infectious mononucleosis-like picture,³⁴ it was considered safe to reinstitute INH alone. One dose of 100 mg. INH was given on the thirty-seventh hospital day, and was followed by severe chills and fever. Finally, three days later, 4 gm. PAS were given alone, and again a similar reaction followed. An attempt was made to desensitize the patient to INH, beginning with 5 mg. and increasing with increments of 5 mg., but this had to be abandoned at the 50 mg. dose because of low grade fever and symptoms of pains in the legs and cervical region followed by chills and fever.

An atypical lymphocyte response occurred with the first attack. This was manifested by a relative and absolute lymphocytosis (90% of 10,000 cells), appearance of atypical lymphocytes (Downey II), and a low grade eosinophilia. The total white blood cell count and relative lymphocyte count varied markedly during the subsequent reactions, and atypical lymphocytes persisted. The heterophil antibody titer was never above 1:8.

The patient was subsequently given SM alone and had no apparent toxicity from it.

Case 2. A 34 year old white male was diagnosed as a case of pulmonary tuberculosis on September 26, 1955, because of infiltration in the right upper lobe with a number of radiolucent areas thought to be cavities. The sputum contained viable tubercle bacilli. The blood count was within normal limits. On October 5, 1955, the patient was started on an antibacterial regimen consisting of INH, 50 mg. three times a day, and PAS, 4 gm. three times a day. On the sixteenth day after this he complained of a peculiar, "weighty" feeling in the back of his head. This was followed the next day by a severe chill and temperature elevation to 102.2° (figure 2). Small, shotty lymph nodes were felt in the cervical region and groins. The white blood cell count at this time was 4,200, with 66% neutrophils, 4% eosinophils and 30% lymphocytes, of which five were atypical.

Since similar reactions had recently been associated with drug therapy, medication was immediately discontinued. The patient became asymptomatic within three days. The white blood cell count was normal after five days.

A test dose of 50 mg. of INH was given six days later. This was followed by the same "weighty" sensation in the patient's occipital region, a chill and temperature elevation to 101° F. Three days after this a test dose of 4 gm. of PAS gave a similar reaction. The patient was then begun on a regimen designed to desensitize him to INH, beginning with 1 mg. daily and increased daily by increments of 1 mg. at first, later 5 mg. He finally reached full dosage of 50 mg. three times a day, with no reaction. Inasmuch as he had some residual liver damage, PAS was omitted entirely and SM substituted.

Case 3. A 23 year old Negro male, with a past history of allergy to penicillin (manifested as asthma) occurring several months before this hospitalization, was admitted August 11, 1955, because of a small infiltration in the right upper lobe. The sputum was negative for tubercle bacilli; the Mantoux test was positive. Treatment for tuberculosis was nevertheless begun with SM, 1.0 gm. intramuscularly twice weekly, and sodium PAS, 12 gm. daily, on August 21, 1955.

Twenty-two days later the temperature rose to 100° F. The patient had mild malaise and pharyngitis. The fever disappeared (figure 3), the only change in therapy consisting of the addition of oxytetracycline orally. On the twenty-seventh day the temperature reached 100.4° F., subsiding in the next two days. On the

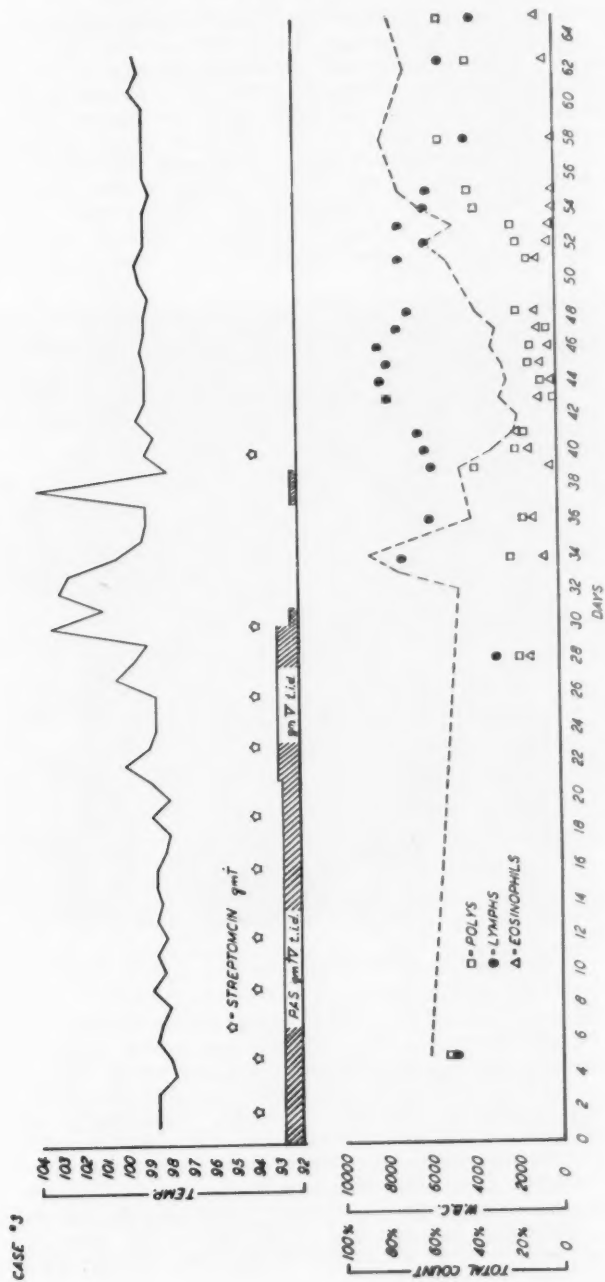


FIG. 3. Relating temperature, medications and white blood count in case 3.

thirtieth day the temperature suddenly rose to 103.4° F., and the patient complained of headache, sore throat and generalized malaise. SM and PAS were stopped. The course of the fever is shown in the chart. On the thirty-second day, small but tender posterior cervical lymph nodes were palpable, and the spleen was slightly enlarged. On this date the total white blood cell count was 4,600 cells per cubic millimeter, with polymorphonuclear neutrophils 28%, lymphocytes 40%, monocytes 9%, and eosinophils 23%. The next day the white blood cell count was 7,300 per cubic millimeter, with 49% lymphocytes, of which almost half (48%) were abnormal and suggested the so-called Downey cells of infectious mononucleosis (figure 4). However, the heterophil antibody titer was normal. A faint macular erythematous eruption was now noted in the axillary areas. Acetylsalicylic acid was meanwhile continued

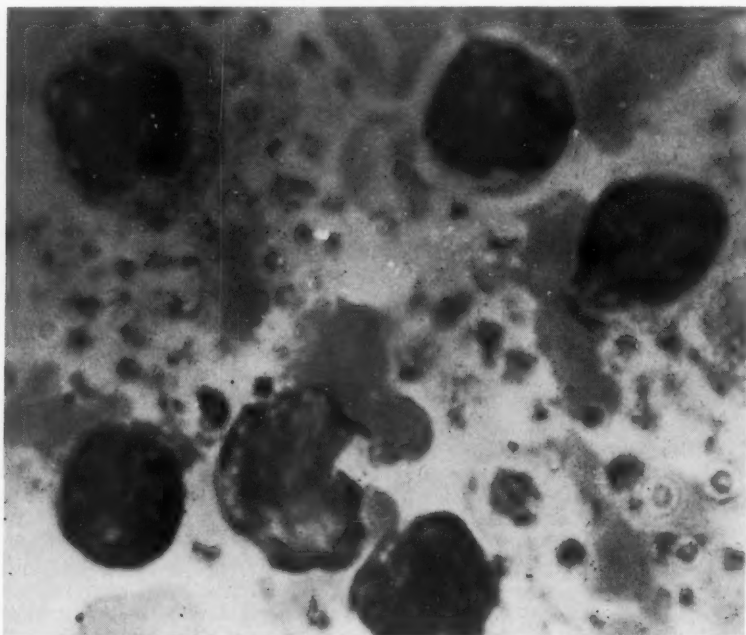


FIG. 4. Photomicrograph of "buffy coat" smear of peripheral blood. The lymphocyte in the upper left corner represents the Type II Downey cell.

for relief of headache. On the thirty-fourth day the total white blood cell count was 8,700 per cubic millimeter; there were 64% abnormal and 8% normal lymphocytes.

By the thirty-seventh day the temperature had been normal for two days, and the patient was feeling well. The white blood cell count was 4,000, with 16% neutrophils, 59% lymphocytes and 21% eosinophils. Splenomegaly was no longer detected. Four grams of PAS were administered that afternoon and repeated the next morning. The second dose was followed in two and one-half hours by chills and fever to 104° F. PAS was again stopped; the patient was now placed on oxytetracycline and erythromycin. A chest x-ray made this day revealed extension of the original infiltration in a perifocal fashion in the right upper lobe. On the thirty-ninth day the temperature was normal and the white blood cell count was 4,500,

with neutrophils 38%, lymphocytes 58% and eosinophils 4%. The hemoglobin was 10.5 gm., and sternal bone marrow aspiration revealed a paucity of neutrophils.

In the next three days the white blood cell count fell to 1,850, with complete disappearance of neutrophils. The patient was afebrile and had few complaints. On the fortieth day he tolerated 1.0 gm. SM intramuscularly without reaction. Two transfusions of 500 c.c. each of freshly drawn whole blood were given on the fortieth and forty-first days. Oxytetracycline and erythromycin were continued. In the course of the next week the white blood cell count rose to 5,000, and the neutrophils to 13%. By the fifty-eighth day the white blood cell count was 8,000, with a normal differential count. Repeated heterophil antibody tests were normal. On the sixtieth day the Mantoux test, using 1:10,000 Old Tuberculin, was 3 plus positive. The fresh infiltration in the right lung gradually cleared in four weeks, leaving the original lesion. At no time did the sputum show tubercle bacilli during this illness.

On October 27, INH, 300 mg. daily, was started and tolerated well, as was acetylsalicylic acid on several occasions. SM in gradually increasing doses, starting with 0.1 gm. on November 15 and reaching 1.0 gm. on November 28, produced no reaction. Attempts to start PAS again were begun on December 19 with 0.1 gm., which produced generalized itching. Two days later, 0.25 gm. was tolerated. On January 3, 1956, 0.5 gm. PAS produced pruritus on the arms and legs, and a headache. On January 10, 1.0 gm. PAS was followed in 12 hours by urticaria on the arms. None of these reactions was followed by febrile or hematologic changes. At this point the patient refused to take any more PAS. A patch test with a 20% aqueous solution of sodium PAS was strongly positive on February 29.

Two months later, while on INH, 300 mg. daily, and SM, 2 gm. weekly, the patient developed a pharyngitis and again was found to have a lymphocytosis, with numerous abnormal lymphocytes (vacuolated cytoplasm and immature nuclei with large clumps of chromatin), although the total white blood cell count was not elevated. Despite cessation of these drugs, the blood changes have persisted, with gradual improvement for six weeks. It has not yet been possible to determine the relation between these changes and INH or SM.

DISCUSSION

As will be described below, similar reactions due to PAS alone have been reported. A discussion of the *combined* features of these reactions will be presented initially.

Allergic response to multiple antigenic substances simultaneously attacking a patient probably occurs with some frequency in such hypersensitive states as pollen, food or dust allergy. However, in allergy to antibacterial agents, we are not aware of similar experience with concurrently administered drugs of unlike molecular configuration in infections other than tuberculosis. The treatment of this disease is of course far different from that in most other infections, chiefly because of longer duration of therapy and the almost universal use of a combination of agents. Possibly analogous to the combined treatment of tuberculosis was the former treatment of syphilis over prolonged periods with combinations of arsenicals and other heavy metals, sometimes given concurrently. However, neither the monograph by Moore¹ nor that by Stokes, Beerman and Ingraham² mentions hypersensitivity reactions elicited by both types of agents, except possibly Herxheimer's reactions which, although resembling constitutional allergic

reactions, were thought to be due to toxic products liberated by the destruction of spirochetes.

Previously, combined drug reactions (that is, reactions to both of a combination of concurrently administered antimicrobial drugs) in the treatment of tuberculosis have been reported by Warring and Howlett,³ Jeffery, Borrie and MacDonald,⁴ Crofton,⁵ Mellette and Agress,⁶ Atwell and Prior,⁷ Sandler,⁸ Hansen and Cleve,¹⁰ Wilder,¹¹ and possibly by Friedman,⁹ Julian³⁹ and Silverman, Swenson and Gray.⁴⁰

Warring and Howlett described one case treated with PAS and SM who developed fever, constitutional symptoms and dermatitis, which were reproduced by test doses of PAS and SM given separately. A test dose of dihydrostreptomycin was tolerated. Two attempts at desensitization to PAS by slowly increasing dosage were failures due to repeated severe reactions.

Jeffery et al. reported one case treated with PAS and SM who developed fever, dermatitis, hepatitis with jaundice, and nephritis; after recovery, the patient manifested positive patch tests to PAS and SM, responded to provocative doses of PAS with reappearance of fever and dermatitis, and to a provocative dose of SM with dermatitis alone.

Crofton mentioned, without detail, that combined reactions to PAS and SM may occur.

Mellette and Agress reported the only case previous to ours (with the possible exception of Friedman's case—*vide infra*) in whom the effect was due to isoniazid and PAS. This patient reacted with fever and abnormal lymphocytes suggesting infectious mononucleosis; separate provocative doses of PAS and INH reproduced the temperature and hematologic changes; subsequently the patient tolerated gradually increasing doses of PAS and INH.

Atwell and Prior described one patient who, during treatment with PAS and SM, developed fever, malaise and dermatitis. Separate provocative doses of PAS and SM reproduced the symptoms and signs; PAS, moreover, produced perifocal pneumonitis about the previous tuberculous lesions as well as pneumonitis elsewhere. Subsequently, the patient tolerated SM but not PAS.

Sandler mentioned five patients with combined reactions to PAS and SM; however, only one of his cited cases appears convincingly like a response to both drugs. This patient was successfully desensitized to both.

The case of Hansen and Cleve may have been an instance of reaction with fever, dermatitis and hepatic necrosis induced by SM and PAS; this patient died with far advanced disseminated tuberculosis. Before death the blood contained abnormal lymphocytes and 23% eosinophils.

Wilder reported one case of neutropenia developing in a child receiving SM and PAS. Each of these drugs in provocative tests reproduced the neutropenia.

Friedman reported a case receiving PAS and INH who reacted with fever, dermatitis, hepatomegaly, jaundice and lymphocytosis with many Downey-type abnormal lymphocytes. Heterophil agglutination tests were normal. Following an attempt to desensitize to PAS, two doses of INH were given; the patient reacted violently, and required treatment with corticotropin. Among other manifestations, he had a perifocal pneumonitis. Whether this case was one of similar reaction to both PAS and INH is not certain.

Julian described a patient receiving SM and PAS who developed fever and dermatitis on the twenty-fourth day of treatment. Later, separate provocative doses of SM and PAS reproduced the same symptoms.

Silverman, Swenson and Gray had two similar cases. The first, treated with SM and PAS for tuberculous pleural effusion, showed fever and dermatitis on the twenty-sixth day, and went on to develop exfoliation of the skin, lymphadenopathy, hepatosplenomegaly, and leukocytosis with eosinophilia and many abnormal lymphocytes. Anuria, hyperglobulinemia, cold agglutinin titer of 1:64, and heterophil antibody titer of 1:112 appeared. After recovery, fever, dermatitis and eosinophilia were provoked by separate test doses of SM and PAS. Their second patient, 41 days after starting treatment with SM and PAS for pulmonary tuberculosis, reacted with fever, leukocytosis, headache and lethargy. The cerebrospinal fluid had 26 lymphocytes per cubic millimeter, and INH was started and tolerated at the height of the reaction. Test doses of SM and PAS, later given separately, produced fever and eosinophilia. Subsequently the patient tolerated gradually increasing doses of PAS.

Quite possibly, many cases of combined reactions have not been recognized because of lack of suspicion and failure to carry out provocative tests in the period soon after the original reaction. Since spontaneous tolerance for one or both of the offending drugs may occur with the passage of time, subsequent tolerance of either is not certain evidence that only one drug was originally responsible for the hypersensitivity response. Also, the well known fact that PAS alone may produce these reactions may lead suspicion away from the companion drug.

Speculation regarding the significance of reactions to combined antimicrobial drug therapy raises interesting points. Jackson¹² has suggested that the mechanism of PAS hypersensitivity manifested as perifocal pneumonitis may be release of a toxic substance (tuberculoprotein) from the infected focus, to which the patient responds specifically in the manner of a Herxheimer reaction, or possibly in the manner of a nonspecific Schwartzman type of reaction. Each of a combination of drugs might so act, thereby leading to a common manifestation of intolerance for both drugs. Favoring such a hypothesis is the frequent occurrence of these combined reactions early during the course of antimicrobial treatment when the tuberculosis

may be exudative, the reported perifocal changes in the lungs and lymph nodes, and the nature of the systemic effects.

In Jackson's second case¹² and our third case, tuberculin testing after the acute reaction did not reveal unusual sensitivity to this agent.

Evidence in favor of a specific allergic sensitivity to the offending drugs consists of the nature of the reactions herein cited—i.e., the dermatologic, hematologic, hepatic, and other manifestations which have all been noted in other drug allergy responses; the frequently positive skin tests, specific for the suspected drugs; the abrupt onset after a period of tolerance of the drug(s); the rapid subsidence of symptoms after cessation of treatment with the intolerable agents; and finally, the response to provocative doses. The success of later desensitization may or may not be evidence of an antigen-antibody type of reaction.³

That severe intolerance should develop rapidly and apparently simultaneously to such dissimilar molecules as PAS and SM or INH must create the suspicion, despite all argument to the contrary, that the hypersensitivity is after all not specific in the sense that anti-PAS and anti-SM or anti-INH antibodies are simultaneously formed. Possibly the answer to the puzzle lies in some common metabolic path for these drugs, or in a disturbed reactive state of the patient that may be excited by various nonspecific but potentially antigenic substances.

INTOLERANCE DUE TO PARA-AMINOSALICYLATES ALONE

PAS has been involved in all of the combined reactions discussed above. It is therefore relevant to review briefly the wide variety of allergic reactions to PAS.

Hypersensitivity reactions to PAS have been frequently mentioned since clinical introduction of this drug in 1946 by Lehmann.¹³ The incidence has been estimated at 2% to 4%.^{3, 14} Although these may take a multitude of forms, review of the literature brings out certain general features. The "benzamine" molecular configuration of PAS, shown in figure 5, is cited by Alexander¹⁵ as appropriate, on the basis of past experience, for production of allergic reactions. It is in the same class of compounds as the sulfonamides and procaine.

The reactions may occur within a few days to a few weeks after initiation of therapy, usually from two to three weeks after start. They are not related to previous allergic manifestations. They may or may not be associated with intolerance to related substances such as acetylsalicylic acid, sodium salicylate, or para-aminobenzoic acid. Positive skin tests of the patch or contact type may or may not occur following reaction to PAS. The only reliable method of proving whether a reaction is due to PAS consists of administering a provocative dose. The initial test dose should be small—0.5 to 1.0 gm.; a fatal response to 5.5 gm. as a test dose has been reported.¹⁶

Tolerance to the drug may be reestablished by the technic of daily increases of dosage, starting with 0.5 gm. or less.^{3, 5, 8}

The most frequently reported forms of hypersensitivity are the appearance of fever alone, or fever with dermatitis of a wide variety of forms.^{3, 14, 17-20} Continued treatment with PAS, despite the warning of fever or less distinct prodromata such as malaise, headache and pruritus, may produce hepatic damage of varying degree up to acute and fatal necrosis, pancreatitis and nephritis.^{4, 14, 21-26} Neurologic manifestations such as myeloradiculoneuritis²⁷ or meningitis²⁸ have been noted. Hematologic disturbances have involved chiefly the leukocytes, manifested as leukopenia or agranulocytosis,^{29, 30, 11} eosinophilia³¹ or lymphocytosis with numbers of abnormal lymphocytes such as have been considered specific for infectious mono-

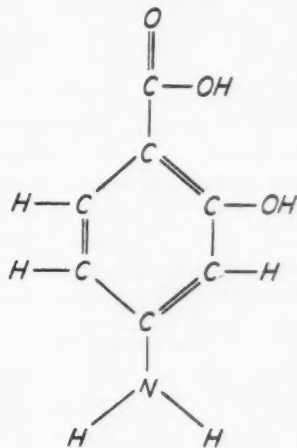


FIG. 5. Para-aminosalicylic acid.

nucleosis (but have recently been shown to occur also in allergic states and virus infections^{32, 33}), accompanied by splenomegaly and lymphadenopathy.^{34, 35} Thrombocytopenia has been reported.³⁶ Pulmonary manifestations have been seen in the nature of perifocal pneumonitis about tuberculous lesions, or transient infiltrations located elsewhere in the lungs, sometimes accompanied by eosinophilia.^{3, 12, 7, 37} Fatalities have been recorded.^{16, 30, 10}

HYPERSENSITIVITY TO STREPTOMYCIN OR ISONIAZID ALONE

Compared to PAS, these drugs are less serious offenders, from the standpoint of producing allergic reactions, when used alone. Among 1,734 patients, allergic reactions severe enough to cause cessation of treatment with SM occurred in only 0.2%, whereas PAS had to be discontinued for the same reason in 1.1%.⁴¹

As pointed out by Alexander,¹⁵ the streptomycin molecule, like PAS, contains a benzene ring with an NH_2 group in the para position. Dermatitis is the most common reaction; among handlers of the drug, contact dermatitis is frequent and serious; among 1,751 patients receiving the drug, 28% had dermatitis of varying forms.³⁸ Severe exfoliative dermatitis may rarely occur.¹⁵ Transient drug fever may occur, usually in the first days of treatment; the temperature may become normal in spite of continued administration of the drug. Much less common reactions are granulocytopenia, thrombocytopenia and aplastic anemia.¹⁵

INH is remarkably free from hypersensitivity reactions. Dermatitis, hepatic dysfunction and granulocytopenia are mentioned by Alexander.¹⁵

SUMMARY

1. Three cases are described with special reference to a drug reaction previously ascribed to PAS. This reaction has been called an infectious mononucleosis-like syndrome, and consists of some or all of the following findings: chills, fever, lymphadenopathy, lymphocytosis with atypical cells, splenomegaly, and evanescent rash.

2. All of the patients here described were receiving PAS at the time of the reaction. Two of them, however, exhibited an additional phenomenon, i.e., the reproduction of a similar clinical picture following a test dose of INH.

3. Attention is invited to possible mechanisms by which two antibacterial drugs, when administered together, may produce the same noxious reaction.

ADDENDUM

Since this manuscript was prepared, Brown et al. (Brown, H., Goldstein, G., and Chapman, G.: Allergy to isoniazid. Successful immunization in two cases, *Am. Rev. Tuberc.* 74, 783, 1956) reported two cases of drug reaction attributed to INH. One possibly was caused by combined reactions to INH and PAS. The interesting suggestion was made that "PAS actually enhances the possibility of a hypersensitivity reaction to any other drug administered at the same time."

SUMMARIO IN INTERLINGUA

Iste articulo describe le occurrentia de un reaction de sensibilitate medicamentose in patientes tuberculotic, reproducibile per le un e le altere del duo medicationes que le patientes recipeva al tempore de lor reactiones original. Le agentes therapeutic in iste casos esseva PAS (para-aminosalicylato de natrium) e INH (isoniazido). Es presentate un revista de duo casos de iste typo de sensibilitate combinate e de un caso in que PAS sol esseva implicade. Le reactiones simulava illos describe alterubi pro PAS sol. Illos se manifestava in algor, febre, exanthema evanescente, lymphadenopathia, splenomegalia, e—in le sanguine circulante—preponderantia lymphatic con cellulas atypic e neutropenia. Le reactiones esseva inducite per doses provocatori de cata un del duo drogas. Dissensibilisation a PAS e INH esseva possibile in un del casos.

Es includite un revista del litteratura. Esseva constatate que inter le citationes de casos de reactiones occurrente in patientes qui recipeva un therapia combinate, solmente 10 o 11 concerneva exemplos de reproducibilitate per ambe drogas in uso individual. Dissensibilisation esseva frequentemente possibile.

Es presentate un breve discussion del varie typos de reacciones de hypersensibilitate e del mecanismos possibile de reacciones combinate. Nos non considera como probable que reacciones identic a grandemente diferente moleculas es causate per le formation de anticorpoes specific contra ille moleculas o que le reacciones es le efecto del liberation de tuberculoproteina, sed il es ver que iste opinion es apparentemente ancora sin supporto experimental. Il es possibile que le solution del problema es a cercar in un coincidentia partial del vias metabolic del drogas in question o in le existentia in le patiente de un stato de reactivitate morbide que pote esser provocate per varie substantias que es non-specific o potencialmente antigenic.

BIBLIOGRAPHY

1. Moore, J. E.: Modern treatment of syphilis, 2nd Ed., 1941, Charles C. Thomas, Springfield, Ill.
2. Stokes, J. H., Beerman, H., and Ingraham, N. R.: Modern clinical syphilology, 3rd Ed., 1944, W. B. Saunders Co., Philadelphia, Pa.
3. Warring, F. C., Jr., and Howlett, K. S., Jr.: Allergic reactions to para-aminosalicylic acid, *Am. Rev. Tuberc.* **65**: 235, 1952.
4. Jeffery, B., Borrie, P., and MacDonald, N.: Acquired hypersensitivity to sodium PAS, streptomycin, and penicillin, *Brit. M. J.* **2**: 647, 1952.
5. Crofton, J. W.: Desensitization to streptomycin and PAS, *Brit. M. J.* **2**: 1014, 1953.
6. Mellette, S. J., and Agress, H.: Toxic reaction to para-aminosalicylic acid and isoniazid accompanied by leukopenia and atypical lymphocytosis, *Am. Rev. Tuberc.* **69**: 824, 1954.
7. Atwell, R. J., and Prior, J. A.: Allergic pneumonitis during chemotherapy for tuberculosis: report of 2 cases due to para-aminosalicylic acid, *Ann. Int. Med.* **42**: 190, 1955.
8. Sandler, A.: Management of hypersensitivity reactions to streptomycin and PAS, *Brit. J. Tuberc.* **49**: 231, 1955.
9. Friedman, E.: Reactions to para-aminosalicylic acid; a case simulating infectious mononucleosis with a transient pulmonic infiltrate, *Am. Rev. Tuberc.* **72**: 833, 1955.
10. Hansen, J. E., and Cleve, E. A.: Fatal hypersensitivity to PAS and streptomycin, *Dis. of Chest* **28**: 577, 1955.
11. Wilder, R.: Two cases of neutropenia in children possibly due to streptomycin and PAS therapy, *Tubercle* **34**: 163, 1953.
12. Jackson, S. L. O.: Acute perifocal reaction in tuberculosis due to PAS, *Tubercle* **35**: 188, 1954.
13. Lehmann, J.: Para-aminosalicylic acid in treatment of tuberculosis; preliminary communication, *Lancet* **1**: 15, 1946.
14. Dixon, W. M.: Toxic reactions to para-aminosalicylic acid, *Brit. J. Tuberc.* **48**: 102, 1954.
15. Alexander, H. L.: Reactions with drug therapy, 1954, W. B. Saunders Co., Philadelphia.
16. Steinger, W. J., Klopfenstein, M. D., and Woodruff, C. E.: Fatal allergic reaction to para-aminosalicylic acid, *Am. Rev. Tuberc.* **69**: 451, 1954.
17. Kierland, R. R., and Carr, D. T.: Reactions to para-aminosalicylic acid, *Proc. Staff Meet., Mayo Clin.* **24**: 539, 1949.
18. Climie, H.: Acquired idiosyncrasy to sodium p-aminosalicylate, *Lancet* **2**: 308, 1950.
19. Korst, D. R.: Severe reactions to para-aminosalicylic acid, *Ann. Int. Med.* **40**: 1011, 1954.
20. Madigan, D. G., Griffith, L. L., Lynch, M. J. C., Bruce, R. A., Kay, S., and Brownlee, G.: Para-aminosalicylic acid in tuberculosis; clinical and pharmacological aspects, *Lancet* **1**: 239, 1950.
21. Steel, S. J.: Acquired sensitivity to para-aminosalicylic acid, *Brit. M. J.* **1**: 415, 1952.
22. McKendrick, G. D. W.: Toxic hepatitis from para-aminosalicylic acid, *Lancet* **2**: 668, 1951.

23. Cuthbert, J.: Acquired idiosyncrasy to sodium p-aminosalicylate, *Lancet* **2**: 209, 1950.
24. Livingston, E. R., and Street, E. W.: Acquired idiosyncrasy to sodium p-aminosalicylate, *Lancet* **2**: 308, 1950.
25. Koester, K.: Acquired hypersensitivity as a life-threatening complication of treatment with PAS, *Ztschr. f. Tuberk.* **106**: 254, 1955.
26. Fergusson, A. G., McIntyre, J. P., and Gemmell, A. R.: Toxic hepatitis and PAS, *Brit. M. J.* **1**: 855, 1952.
27. Bulley, K. G.: Near-fatal shock from PAS followed by Guillain-Barré syndrome, *Am. Rev. Tuberc.* **69**: 455, 1954.
28. Bridge, E. V., and Hoffman, G. N.: Reaction to para-aminosalicylic acid simulating tuberculous meningitis, *Am. Rev. Tuberc.* **64**: 682, 1951.
29. Mahrer, R. A., and Maret, R.: Agranulocytosis complicating PAS and streptomycin therapy, *U. S. Armed Forces M. J.* **6**: 1193, 1955.
30. Muri, J.: Lethal p-aminosalicylic acid intoxication, *Nord. med.* **47**: 155, 1952.
31. Read, J.: On the occurrence of eosinophilia in tuberculosis treated with antibiotics, *Brit. J. Tuberc.* **49**: 134, 1955.
32. Randolph, T. G., and Gibson, E. B.: Blood studies in allergy: presence in allergic disease of atypical lymphocytes and symptoms suggesting recovery phase of infectious mononucleosis, *Am. J. M. Sc.* **207**: 638, 1944.
33. Litwins, J., and Leibowitz, S.: Abnormal lymphocytes ("viocytes") in virus diseases other than infectious mononucleosis, *Acta haemat.* **5**: 223, 1951.
34. Lichtenstein, M. R., and Cannemeyer, W.: Severe para-aminosalicylic acid hypersensitivity simulating mononucleosis or hepatitis, *J. A. M. A.* **152**: 606, 1953.
35. Sjoukes, P.: Symptoms resembling infectious mononucleosis, following administration of p-aminosalicylic acid, *Nederl. tijdschr. v. geneesk.* **96**: 2001, 1952.
36. Wurzel, H. A., and Maycock, R. L.: Thrombocytopenia induced by sodium para-aminosalicylic acid, *J. A. M. A.* **153**: 1094, 1953.
37. Tuchman, H.: Loeffler's reaction to para-aminosalicylic acid, *Am. Rev. Tuberc.* **70**: 171, 1954.
38. Bunn, P. A., and Westlake, R. E., in Waksman, S. A.: Streptomycin, 1949, Williams and Wilkins, Baltimore, p. 524.
39. Julian, D. G.: Acquired sensitivity to streptomycin and sodium PAS, *Brit. M. J.* **2**: 476, 1952.
40. Silverman, J. D., Swenson, E. W., and Gray, J. A. C.: Simultaneous hypersensitivity to streptomycin and para-aminosalicylic acid, *Dis. of Chest* **30**: 103, 1956.
41. Schwartz, W. S., and Moyer, R. E.: Incidence of severe toxic reactions to streptomycin and para-aminosalicylic acid, Transactions of Eleventh Conference on Chemotherapy of Tuberculosis, Veterans Administration, p. 196, 1952.

PROBLEM IN THE DIAGNOSIS OF LEUKEMIA *

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INTRODUCTION

LEUKEMIA as a clinical entity has been recognized for many years. It is identified by various combinations of adenopathy, hepatosplenomegaly, anemia and varied bleeding tendencies, as well as by other factors such as infection and necrosis. When the disease is full-blown clinically the bone marrow findings should be conclusive. Frequently they are not performed because of the obvious clinical picture and the appearance of the peripheral blood. According to Wintrobe,¹ "Hyperplasia is usually diffuse and widespread throughout the marrow spaces"; however, it is conceivable that it may not involve all of the marrow spaces at all stages of the disease. The duration and nature of spread of the leukemic process may be a controlling factor.

In early cases of leukemia it is important to differentiate it from other serious and confusing diseases, such as, among others, agranulocytosis, aplastic anemia, myeloid metaplasia or hypersplenism. At this point in the picture a differentiation by means of the bone marrow is considered a very helpful procedure and frequently confirms or denies the eventual diagnosis. Wintrobe¹ states: "Marrow examination during life achieves its greatest usefulness in differentiating these diseases, that is leukemia, in the leucopenia state." This would lead one to believe that as a rule the bone marrow changes precede the clinical changes and should be diagnostic at most times if carefully performed and competently observed by experienced operators. Yet this is not always the case, as is seen in the recent reports in the literature. Block and Jacobson² report 12 cases of acute leukemia observed for from about three to 27 months prior to the time when an exact diagnosis of leukemia could be made. Following the diagnosis the patients died within a period of one to four months. This report would indicate that the disease was present and clinically active, as well as documented by competent physicians, before a bone marrow picture was evident. It would seem as though the diagnosis of leukemia was really made in a terminal state, rather than early or midway in the disease. In these cases,² anemia was an outstanding feature and was unresponsive to the various means of therapy. Obviously, as we look back on these cases, leukemia was present but indistinguishable from other mimicking diseases. Andre et al.³ reported a case of a 38 year old white male who had an unexplained neutropenia for 18 months, followed by an anemia that also failed to respond to the hematinics used. Two

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separate bone marrow aspirations done during the acute course of the illness revealed hypoplasia, but a diagnosis of leukemia could not be made. Three months prior to the death of the patient a typical diagnostic hyperplastic, blastic marrow was noted. The patient succumbed with the usual leukemic signs and symptoms.

The cases about to be reported were equally difficult diagnostic problems. Although the clinical course, signs and symptoms were very suggestive of a leukemic process, the diagnosis could not be made until a terminal state had been reached. These cases were followed very closely, and the pitfalls and problems that arose are stated herein.

CASE REPORTS

Case 1. A 68 year old white female housewife was admitted to the St. Elizabeth Hospital on January 4, 1950, because of a recent one-week history of marked weakness, anorexia, headache, pallor and recurrent, moderately severe nasal and rectal hemorrhage. There was no history of exposure to noxious chemicals, allergic reactions or drug ingestion. There had been no previous evidence of bleeding or jaundice, or even bleeding tendencies. The patient was a moderate diabetic who had been controlled with diet alone for the last five years. Her past history revealed only a cholecystectomy for chronic cholecystitis in 1948, at which time her appendix was also removed. No unusual bleeding or anemia had been noted at the time of surgery. Physical examination on admission revealed an acutely ill adult white female with marked pallor and evidence of dried, caked blood about the nasal orifice. Respirations were 24; temperature 103° F.; blood pressure, 200/100 mm. of Hg; pulse, 120. The positive physical findings included moist râles in both lung bases, a moderate grade II systolic murmur, heard over the entire precordium but loudest at the apex, 2 plus pedal edema, a soft but tender abdomen with no localization of spasticity, and complete absence of a palpable liver or spleen or enlarged nodes. Rectal examination revealed fresh blood on the examining finger, but no masses or hemorrhoids. Admission laboratory studies revealed: Urine: specific gravity, 1.024, with 4 plus glucose, traces of albumin, and 3 plus acetone; fasting blood sugar, 330 mg.%; red blood cells, 2.3 million, with a hemoglobin of 8 gm. The white blood cells numbered 3400 per cubic millimeter, with the following differential: polymorphonuclears, 28%; stabs, 12%; juveniles, 2%; myelocytes, 2%; lymphocytes, 56%; and one nucleated red cell per 100 white blood cells. Platelets were markedly diminished on the smear. Serologic test for syphilis was negative. Her blood type was O, Rh positive.

The clinical course and treatment of the patient were as follows: She was given insulin and fluids as well as electrolytes to combat the obvious diabetic acidosis. She also received antibiotics and was transfused with 1,000 c.c. of whole blood on January 15. The febrile reaction responded very nicely, and she became afebrile. The diabetic status and acidosis also responded quite easily and was no problem during the remainder of the hospital stay. The bleeding from the anus and nose gradually subsided until January 22, at which time it recurred with greater intensity. The patient continued to receive periodic transfusions, which seemed to improve her clinical condition in spite of the fact that the red blood cell response was poor. Bone marrow aspiration on January 23 revealed erythroid hyperplasia, total absence of megakaryocytes, marked decrease in platelets, but no diagnostic change in the myeloid elements. The peripheral platelet count hovered around 15,000. The diagnosis at this time was toxic depression of the megakaryocytic and myeloid elements and a compensatory hyperplasia of the red blood cells in response to the active bleeding

process. The reticulocyte count was 3%. The patient was kept on penicillin during most of her hospitalization because of the leukopenic state that persisted. She experienced an essentially afebrile course except for occasional short elevations of temperature. Repeated red blood counts varied from 1.65 million to 2.7 million, depending upon the length of time from the last transfusion. The reticulocyte counts were low except for one occasion, when it was 3%. Bleeding time varied from four minutes to 15 minutes, which would be considered elevated in our laboratory. Other studies, such as the gastrointestinal series, chest x-rays, and x-rays of the skull, ribs and long bones were normal. Bence Jones studies were also negative. Another bone marrow aspiration, performed on February 9, revealed a total nucleated cell count of 160,000 per cubic millimeter, with no megakaryocytes seen. The differential once more revealed moderate erythronormoblastosis of 90%. Platelet count was low and the myeloid cells were not diagnostic. The patient continued to show bleeding from the anus, vagina, nose, mouth, and possibly the stomach and lungs. These bleeding periods were lengthy and quite severe, but at no time was the prothrombin time anything but normal. Petechiae also were frequent. The Rumpel-Leede test was positive. In desperation, the gamut of hematinics, including vitamin B₁₂, vitamin C, vitamin K, rutin, liver extract, iron, etc., was given the patient, but nothing seemed to help her. Her condition was precarious during the entire hospital course. Gastric analysis performed March 1 revealed no free hydrochloric acid and moderate amounts of blood. The white blood cell count was leukopenic, varying from 1,400 to 4,000, with a differential that showed a predominance of lymphocytes. Because of the marked lymphocytosis, the pathologist felt that a diagnosis of lymphocytic leukemia was justified. A bone marrow aspiration performed on March 30 revealed marked erythronormoblastosis, with a moderate increase in myeloblasts (7.5%) and promyelocytes (10%), with a maturation arrest of other granulocytic elements. A definite diagnosis of leukemia could not be made on the basis of this bone marrow, but the suspicion was there. On April 10 the peripheral smear differential was diagnostic for the first time and revealed 5% myeloblasts. This was the first time in the patient's hospital stay that one could be certain of the diagnosis. Peripheral smears done prior to this time did not reveal the obvious myeloblasts. The patient did not survive very long after this, and pursued a very rapid downward course until her death on May 22. No postmortem examination was permitted, but the bone marrow and peripheral smears following April 10 showed moderate increases in myeloblasts, supporting the diagnosis of subacute myeloblastic leukemia.

Comment: This patient entered the hospital suffering from a blood dyscrasia, and followed a progressively downward course that failed to respond to any form of medication. The differential diagnosis included toxic depression of the bone marrow, aplastic anemia, metastatic carcinoma, hypersplenism and leukemia. She entered the hospital January 4, 1950, but it was not until April 10 that a distinct diagnosis could be made on the basis of the bone marrow and peripheral smears. Following April 10 the peripheral smears revealed 4 to 6% myeloblasts, as well as a few nucleated red blood cells per 100 white blood cells. At no time during her course was the liver or spleen palpable, nor were any nodes enlarged or suspicious enough to be removed for biopsy. The case was seen in consultation with various pathologists and hematologists while the patient was still alive, and was a controversial diagnostic problem until the distinct marrow and peripheral smears. Yet to the casual observer this case looked like leukemia, and responded like

leukemia to the modalities of therapy which were instituted. Although leukemia was suspected after the initial work-ups, it could not be positively identified until she became terminal.

Case 2. A 66 year old white male ditch digger of Italian extraction was admitted to the Alexian Brothers Hospital on August 11, 1952. His chief complaints were weakness, pallor, easy bruising and shortness of breath. These symptoms had been very gradual in onset over a period of two or three months. The past history was normal. There was no family history of jaundice or blood dyscrasia. There was no history of unusual drug ingestion or industrial exposure to noxious chemicals. He had had no febrile course or history of animal bites. He had been apparently healthy most of his life, and had not consulted a physician until his present illness.

Physical examination revealed a pale, acutely and chronically ill adult white male with some shortness of breath upon mild exertion. Blood pressure was 120/70 mm. of Hg; pulse, 80; respirations, 20; temperature, 98.6° F. The positive physical findings included a few small hematomas of the back and arms, and 1 plus pitting edema of the ankles, but no hepatosplenomegaly or enlarged nodes. Laboratory results upon admission were as follows: red blood cells, 1.3 million; white blood cells, 5,400; hemoglobin, 4.25 gm. The white blood cell differential included segmented neutrophils, 46%; stabs, 3%; eosinophils, 4%; lymphocytes, 40%; basophils, 1%; monocytes, 6%. The blood type was O, Rh positive. The red cells showed marked achromia, anisocytosis, poikilocytosis, polychromasia and stippling, and there were 9 normoblasts per 100 white blood cells. The platelet count was markedly depressed (to 15,000). Urinalysis revealed 25 to 30 red blood cells per high power field, but was otherwise normal. Urobilinogen in the urine was negative both qualitatively and quantitatively. Icteric index, 5.1; total protein, 6.1 gm.%; A/G ratio, 3.0. Blood Mazzini test was negative. Cephalin flocculation was 1 plus, and thymol turbidity was 1. Bone marrow aspiration on August 20 revealed a marked hyperplasia of all elements, including megakaryocytes. The differential count was as follows: myeloblasts, 1%; neutrophilic myelocytes, 15%; segmented neutrophils, 36.4%; mature eosinophils, 3%; erythroblasts, 3%; normoblasts, 26.5%. Immature megakaryocytes were plentiful but the platelets were very sparse. An electrocardiogram was normal except for a sinus tachycardia of 110.

The clinical course was as follows: Patient was given 500 c.c. of blood shortly after admission, without any significant change in the blood count, platelets or the elevated bleeding time. Reticulocyte count was 0.9%. Red blood cell fragility was increased, with hemolysis starting at 0.56 and completed at 0.42. Nucleated red blood cells were seen in the peripheral blood on almost all occasions, and there were repeated hematomas of the arms, legs and back. On August 22 the patient was started on ACTH, 20 units intramuscularly four times a day, as well as a low sodium diet. His course was downward, and late in August the tip of the spleen could be palpated. His response to ACTH was very questionable. At this time a diagnosis of hypersplenism was entertained, and it was decided to splenectomize the patient. At surgery the spleen was friable and enlarged to 625 gm., and was removed with great difficulty. There was marked oozing from the splenic fossa as well as the abdominal incision. The surgeon had to work quite rapidly because of the apparently poor condition of the patient. Following surgery there was continued oozing from the incision. The patient had a very stormy postoperative course in spite of many transfusions of blood. The day after surgery the patient's red blood count was 3.8 million; hemoglobin, 10.5 gm.; white blood cells, 14,200, with a normal differential; platelets, 36,800. This was after numerous transfusions. One week later the blood elements had shown a significant drop, and there was no change in the low platelet count or the bleeding tendency. On September 27 the red blood cells were 2.4 million; hemoglobin, 7.25

gm.; white blood cells, 5,100, with a differential count as follows: segmented neutrophils, 46%; juveniles, 1%; myelocytes, 1%; immature lymphocytes, 1%; lymphocytes, 51%. Numerous normoblasts were seen in the peripheral blood. Surgical recovery was finally complete, and the patient was discharged to his home after frequent transfusions. Pathologic report on the spleen revealed numerous foci of myelocytes, polymorphonuclears and myeloblasts in the sinusoids, and the diagnosis was myelocytic leukemia of the spleen. The patient's downward course continued, and he was re-admitted to the hospital in October and in December of the same year. His peripheral blood picture presented numerous myeloblasts as well as increased lymphocytes and normoblastosis. A repeat bone marrow performed November 28 was reviewed by three prominent hematologists, with the following comment: "The bone marrow is surprisingly normal, but the peripheral blood is suggestive of myeloblastic leukemia." A definite diagnosis could not be made. The patient died on January 6, 1953, in spite of repeated blood transfusions and other symptomatic care. The peripheral blood continued to show myeloblasts and many nucleated red blood cells per 100 white blood cells. No postmortem examination was performed.

Comment: This patient's clinical course and history were indicative of leukemia, but the bone marrow and peripheral smears failed to define the diagnosis until the terminal state. Yet the spleen was infiltrated with leukemic tissue, so that one could assume that the disease was widespread even at that time. Certainly it was clinically widespread to all intents and purposes. Still, the last bone marrow, performed November 28, approximately six weeks prior to death, was "surprisingly normal," as reviewed by a very competent hematologist.

DISCUSSION

A review of the literature reveals that other investigators have noted the occasional discrepancy between the state of clinical leukemia and the bone marrow interpretation, such as occurred in the two cases already reviewed in this article. Meacham and Weissberger⁴ describe a syndrome consisting of severe anemia, hyperactive bone marrow, neutropenia and thrombocytopenia, observed in 11 patients, eight of whom developed leukemia at a later date. Although the authors do not state it as such, it is obvious that the disease process described is leukemia but disguised beyond recognition. These cases were judged to be hypersplenism, but the eventual picture was neoplastic. They warned of the possibility of misdiagnosis in cases such as these.

Bernard⁵ believes that there is a discrepancy between the state of the blood and the state of the hemopoietic organs. According to classic hematology, the leukoses are systemic diseases which in some cases, even at the very beginning, involve all of the hemopoietic system. The author believes that leukemic lesions may be strictly localized, and that there is no uniform and simple correlation between the state of the blood-generating organs and the simultaneous blood picture. Evidently there is a complex and puzzling interaction of various factors, many of which are unknown.

Danopoulos et al.⁶ reported on three cases of acute leukemia in whom the

site of origin of the disease was the liver or spleen rather than the bone marrow. He states that in these cases the bone marrow was essentially normal until the terminal state. He believes that there may be cases of leukemia in whom the disease starts and continues for a variable length of time in extramedullary organs.

Dreyfus and Bessis⁷ report on 17 cases in whom there was terminal leukemia preceded by myeloid aplasia. In all of their cases there were marked anemia and pancytopenia as well as a clinically sick individual, but the diagnosis could not be established with certainty for a variable length of time. The marrow was variable, but not diagnostic.

Bernard⁸ discusses a state of leukemia which he calls the preleukoblastic state. This stage may last for a variable length of time, and during this period bone marrow aspirations from all sites fail to distinguish the disease. After a period of time, varying from months to years, the clinical and bone marrow disease becomes manifest and there is no particular diagnostic problem.

The bone marrow is considered an important tool in the use and diagnosis of leukemia. It owes its popularity to the ease of technic, the paucity of serious side reactions, and the ability to observe the pathologic process under the microscope. It is used frequently in cases of anemia or suspected blood dyscrasia, as well as in a variety of associated conditions. Classically, leukemia is ruled out or confirmed on the basis of an adequate bone marrow investigation which has been interpreted by a trained individual.

Yet personal experience plus recent findings and reported cases have changed the problem so that there are occasional situations where a diagnosis was "missed" because of an apparently normal marrow. There is obviously a lapse of time during which the diagnosis is obscured, but at present this does not jeopardize the life of the patient, because there is no cure for leukemia and haste is not critical. However, if the medical profession is able to arrive at a cure for leukemia, it is possible that early cases will be more amenable to treatment than late or terminal cases. Then haste in making a diagnosis will become paramount.

There are many interacting factors that influence the course of leukemia, many of which are unknown. Erf⁹ defines leukemia as an abnormality of the growth maturation of the reticuloendothelial system. There is an apparent increase in the incidence of this disease, and the suggested causes are many. They include deficiencies, excesses of some stimulating agent, hormonal imbalances, viral causes, etc. The disease obviously passes through various stages of evolution, either continuous or recurrent, but the final stage is rapid and continuous. Whether the disease starts as an aplasia or hyperplasia is still a question. It may be that aplasia is an early stage of leukemia and, by damaging the marrow, may set up a favorable ground for the secondary development of leukemia. These are puzzling questions that are still unsolved, but the alert physician is always trying to find a new and obscure

factor that may help in the diagnosis as well as the treatment of a disease. The cases reviewed in this article can be added to those reviewed by others which demonstrate the fact that leukemia may occur in a greatly disguised form and still pursue its clinical course.

CONCLUSIONS

This paper has reported two fairly well substantiated cases of subacute leukemia in whom follow-up studies and careful clinical studies during the course of the disease failed to provide a clear-cut diagnosis until the terminal state. The clinical picture was so suggestive of this disease that it was usually included in the differential diagnosis but excluded because of the paucity of bone marrow and peripheral smear findings. The physician waiting for scientific confirmation was one of the last to agree to the diagnosis. The problem these two cases present has been noted in all parts of the world, and more instances are being reported from large and well attended clinics. There may be an explanation for this phenomenon, but in the meantime we must recognize that there is such an entity, and that a patient may have leukemia in the absence of diagnostic bone marrow findings.

SUMMARY IN INTERLINGUA

Leucemia ha essite recognoscite como entitate clinic durante multe annos. Le diagnose se basa super le manifestation del morbo insimul con varie constataciones laboratorial. Le plus importante de istos resulta del aspiration medullari. Le aspiration medullari se ha provate utilissime in le differentiation de morbos que imita leucemia, per exemplo reactiones leucemoide, anemia aplastic, hypersplenismo, agranulocytosis, e metaplasia myeloide. Le casos hic presentate demonstra un discrepantia inter le stato clinic e le medulla ossee. In ambe casos le patientes habeva evidentemente avanzate a grados moderate in le processo leucemic, sed le studio del medulla ossee non resultava in un confirmation positive del diagnose usque le stadio terminal habeva arrive. In un del patientes le condition esseva interpretate como hypersplenismo, sed al operation il esseva constatate que le patiente habeva leucemia myelocytic del splen. Isto occurreva al minus tres menses ante que myeloblastos esseva notate in le sanguine peripheric. Le medulla ossee, examinate un mense ante morte, esseva sorprendentemente normal in iste caso.

Le exemplos prova que le processo leucemic non implica le medulla in omne casos, e le diagnose es a vices a facer in le absentia de un confirmation per le medulla. Altere reportos in le litteratura pare confirmar iste inusual constataciones.

BIBLIOGRAPHY

1. Wintrobe, M. M.: Clinical hematology, 3d Ed., 1952, Lea and Febiger, Philadelphia.
2. Block, M., Jacobson, L. D., and Bethard, W. F.: Preleukemic acute human leukemia, *J. A. M. A.* **152**: 1018-1028, 1953.
3. Andre, L., Marty, J., Respe, R., and Morichman-Beuchant, J.: A case of acute leukemia preceded by neutropenia, of 18 months duration, *Bull. et mém. Soc. méd. d. hôp. de Paris* **69**: 417-421, 1953.
4. Meacham, G. C., and Weissberger, A. S.: Early atypical manifestations of leukemia, *J. Lab. and Clin. Med.* **42**: 923-924, 1953.

5. Bernard, J., Tubiana, M., and Mathe, G.: Discrepancies between the state of the blood and that of the hematopoietic organs in the leukemias, *Semaine d. hôp. Paris* **28**: 3726-3735, 1952.
6. Danopoulos, E., and Angelopoulos, B.: Der extramedulläre Beginn der akuten Leukämien; Beobachtungen und Schlüsse bei 3 eigenen Fällen, *Med. Klin.* **49**: 1947-1950, 1954.
7. Dreyfus, B., and Bessis, M.: Acute leukemia preceded by myeloid aplasia, *Sang* **25**: 787-797, 1954.
8. Bernard, J., and Boron, M.: The preleucoblastic anemias of acute leukemias, *Sang* **25**: 797-825, 1954.
9. Erf, L. A.: Leukemia—theory and therapy, *Seminar* **16**: 2-6, 1945.

TRENDS IN CARDIOVASCULAR SYPHILIS*

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INTRODUCTION

CARDIOVASCULAR syphilis remains a serious threat to life and health despite its decreasing incidence and the increasingly efficient armamentarium of the cardiologist. This study was undertaken to determine the prevalence of cardiovascular syphilis in similar hospital populations, to describe changing methods of diagnosis and treatment, and to determine, insofar as possible, the effect of such treatment on the course of the disease.

According to the records of the Los Angeles County Hospital for 1945-1954, 1,002 persons were admitted during that period with diagnoses of "cardiovascular syphilis," "blood vessel syphilis" and/or "aneurysm of thoracic aorta." Charts of 954 of these patients were sufficiently detailed for use in compiling this report.

DESCRIPTION OF PATIENTS: RACE,† SEX AND AGE

Included in the 954 patients were 723 men (491 white, 232 colored) and 231 women (121 white, 110 colored).

On the average, the colored patients within this study were about five years younger than the white patients at the time the diagnosis of cardiovascular syphilis was made, mean age of the white patients being 60.6 years, mean age of the colored patients, 55.8 years. In white persons cardiovascular syphilis most commonly was diagnosed between 60 and 69 years of age (both men and women); but in colored men the greatest incidence fell between the ages of 50 and 59, and in colored women the condition was discovered most often between 40 and 49.

INCIDENCE COMPARED WITH NATIONAL FIGURES

United States Public Health Service statistics¹ show a gradual decrease in cases of early syphilis from 1947 to 1953. However, reported cases of late and latent syphilis have not followed this pattern, but remained fairly constant in the years 1945 to 1950.²

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† The colored patients in this study were an admixture of white and Negro; the white persons were mostly of Mexican descent.

Investigating the prevalence of cardiovascular syphilis among persons in New England, White³ found that the relative incidence had dropped from 3.9% of all cases of cardiac disease in 1925 to only 1.0% in 1950.

The relative incidence of persons with cardiovascular syphilis admitted to the Los Angeles County Hospital also dropped during the period under study: admissions of patients with cardiovascular syphilis decreased from 0.32% of all admissions in 1946-47 to slightly over half (0.17%) in 1953-54.

DIAGNOSIS OF CARDIOVASCULAR SYPHILIS

In the study reported herein, diagnosis of cardiovascular syphilis was based upon presence of characteristic cardiovascular lesions plus (a) a history of syphilitic infection; (b) a history of antisyphilitic treatment, or (c) a positive serologic test for syphilis. Evidence of rheumatic heart disease was not considered to be inconsistent with a diagnosis of cardiovascular syphilis. Roentgenologic evidence of aortitis was of great help and in many cases was conclusive. About 27% of aortitis cases first were recognized at autopsy, as were 18.5% of cases of syphilitic aortic aneurysm and about 1.2% of cases of aortic insufficiency.

INTERVAL BETWEEN INFECTION AND DIAGNOSIS

Only 275 patients (28.8%) were able or willing to give the date of their initial infection. Four times as many men as women gave information as to date of infection.

The mean number of years between initial infection and diagnosis of cardiovascular syphilis was approximately 29. This time interval is somewhat greater than that mentioned by Anderson,⁴ who found signs of syphilitic aortitis in patients an average of 20 years after the initial infection. Other investigators⁵ report recognition of 45% of cases of cardiovascular syphilis in the second decade after infection, and recognition of an additional 30% in the third decade of the disease.

BLOOD SEROLOGY: EFFECT OF TREATMENT

Serologic reactions were positive or repeatedly doubtful in 82% of cases studied. As might have been anticipated from reports of other investigators,⁶ the effect of penicillin therapy on serologic reactions was disappointing: positive reactions became negative following penicillin therapy in only 4.6% of penicillin-treated cases. Treatment with bismuth and/or arsenicals and malaria made serologic reactions negative in 2.4%; treatment with bismuth and/or arsenicals and penicillin caused a similar change in 1.3% of treated cases.

In 23% of cases studied, spinal fluid reactions for syphilis were positive.

RHEUMATIC HEART DISEASE

Rheumatic heart disease was found in 73 of the 954 patients under study (7.5%).

COMPLICATIONS

The most frequent complication of cardiovascular syphilis is congestive heart failure, present in 67.5% of the patients under study, and especially common in persons with syphilitic aortic insufficiency. Commonly, congestive heart failure starts with failure of the left ventricle; if the patient does not die in acute left heart failure, the condition progresses, within a matter of a few weeks to several years, to failure of the right side of the heart.

Other frequent complications of cardiovascular syphilis are hypertension, angina pectoris with or without myocardial infarction, and rupture of an aortic aneurysm.

ROENTGENOLOGIC FINDINGS

Roentgenologic evidence of syphilitic cardiovascular disease was present in 91.2% of cases examined, and proved particularly helpful in diagnosis of uncomplicated syphilitic aortitis and aneurysm.^{7a, 7b}

ELECTROCARDIOGRAPHIC FINDINGS

No typical electrocardiographic pattern is apparent.⁶ However, electrocardiograms were normal in less than 4% of the cases examined. Left axis deviation, left ventricular hypertrophy, atrioventricular conduction disturbance and intraventricular conduction disturbance were the abnormalities noted most frequently.

TREATMENT

Treatment for cardiovascular syphilis was in transition from arsenicals and bismuth compounds to penicillin in the years under study (1945 to 1954, inclusive). Potassium iodide was in common use, particularly as a supportive drug in older patients before and following courses of bismuth and arsenicals.

Only in a small percentage of cases, impossible to determine with certainty, had patients received adequate treatment closely following the time of infection. Indeed, only 29% admitted knowing the actual or approximate date of infection. Fifty-five per cent of the patients had received no anti-syphilitic treatment before the diagnosis of cardiovascular syphilis was established.

To gauge the efficacy of (a) adequate early treatment, and (b) treatment with penicillin, with or without bismuth compounds, the number of months lived following diagnosis of cardiovascular syphilis was chosen as an objective criterion (table 1).

TABLE 1
Influence of Treatment on Length of Life Following Diagnosis of Cardiovascular Syphilis

Number of Patients	Treatment Prior to Current Hospitalization (for Initial Infection or for Cardiovascular Lesions)	Treatment with Current Hospitalization after Diagnosis of Cardiovascular Syphilis	Months of Life after Diagnosis
White Patients			
75	No treatment	No treatment	15.0
31	Inadequate (bismuth and arsenic)	No treatment	23.9
26	Adequate (bismuth and arsenic)	No treatment	59.6
40	No treatment	Inadequate (penicillin)	11.5
16	No treatment	Significant (penicillin)	18.2
27	No treatment	Adequate (penicillin)	12.6
19	Quality of treatment unknown (bismuth and arsenic)	Inadequate (penicillin)	47.2
14	Quality of treatment unknown (bismuth and arsenic)	Significant (penicillin)	45.0
21	Quality of treatment unknown	Adequate (penicillin)	25.3
5	No treatment	Adequate treatment with penicillin after preparation with bismuth	14.4
Colored Patients			
30	No treatment	No treatment	17.3
24	Inadequate (bismuth and arsenic)	No treatment	39.7
7	Adequate (bismuth and arsenic)	No treatment	55.0
10	No treatment	Inadequate (penicillin)	7.3
8	No treatment	Significant (penicillin)	25.8
12	No treatment	Adequate (penicillin)	21.0
10	Quality of treatment unknown (bismuth and arsenic)	Inadequate (penicillin)	55.6
8	Quality of treatment unknown (bismuth and arsenic)	Significant (penicillin)	36.4
19	Quality of treatment unknown (bismuth and arsenic)	Adequate (penicillin)	24.6
7	No treatment	Adequate treatment with penicillin after preparation with bismuth	31.2

In the table, penicillin dosage under 2.4 million units is described as "inadequate"; between 2.4 and 6.0 million units, as "significant"; and over 6.0 million units, as "adequate."

Persons in this study who developed cardiovascular syphilis despite adequate treatment of the initial infection (with arsenicals and bismuth) lived two to three times as long after developing cardiovascular lesions as did patients receiving no treatment of the initial infection.⁶

Length of life following diagnosis of cardiovascular syphilis was not far different in cases receiving penicillin alone after lesions had developed, and in cases receiving no treatment whatsoever, probably because most patients who received penicillin first received the antibiotic rather a short time before death. Several investigators have suggested⁸ that penicillin is impotent against complications of syphilitic aortitis, but members of a second group⁹ feel that the specific inflammatory process is reversible with penicillin treatment.

However, the impression remains that adequate treatment with penicillin, presently the most potent of all spirillicidal preparations, will effectively forestall development of cardiovascular syphilis. If some patients develop

cardiovascular syphilis notwithstanding adequate penicillin therapy (penicillin does not afford a biologic cure¹⁰), the life expectancy of such patients presumably would be equal to if not better than the life expectancy of patients adequately treated with bismuth or arsenic compounds shortly after infection.

This study furnishes no evidence that penicillin is in any way harmful. Indeed, in this study as in others, many patients with congestive failure and angina pectoris improved after treatment.⁸ Our material disproves the old saying that "patients with cardiovascular syphilis go into heart failure only once," for congestive failure was treated successfully in many patients with a combination of digitalis and penicillin, and the patients—fully compensated when discharged—returned time after time in failure because the physician's instructions had been ignored. Modern medical care and proper cardiac medication are perhaps more important in restoring compensation in these patients than antisyphilitic therapy is.

Untoward reactions to penicillin therapy were rare: in 12 instances body temperature was elevated up to 2° F. for periods of one to 14 days, starting on the third or fourth day of treatment. No typical cases of therapeutic shock or Jarisch-Herxheimer reaction were observed after treatment with penicillin. Therapeutic paradox was observed in two instances after treatment with bismuth compounds: in one case after treatment with bismuth compounds and penicillin, and in one case after treatment with penicillin alone. In a few additional cases the patient's condition worsened during or immediately after penicillin treatment, due to additional complications such as hypertension.

Deterioration of a patient's condition during or immediately after treatment with penicillin—enlargement or initial appearance of an aneurysm, for example—might be caused by the severe inflammatory reaction noted by some investigators,¹¹ which reaction, with its exudate and swelling, might cause weakening of diseased aortic walls. Swelling around coronary ostia might disturb coronary circulation and bring on ischemic retrosternal pain. Even without causing anginal pain, diminished coronary circulation presumably could result in diminution of cardiac reserve and thus initiate or increase congestive failure. However, other authors¹² do not report changes of any considerable magnitude in cardiovascular lesions of syphilitic origin during penicillin treatment.

Instances of deterioration in the patient's condition several months after completion of penicillin therapy could not have been due to the direct action of penicillin, a short-acting antibiotic with lytic action on spirochetes.¹³ Late effects of penicillin may result either from inadequate dosage—in which case the spirochetes would not be destroyed and the disease would progress unchecked—or, if dosage was adequate, from healing of the lesion with scarring. Such scarring might produce anatomic and functional changes with appearance of pathologic signs. Some investigators do not agree¹² that extensive fibrosis may result from absorption of syphilitic exudate.

Effects of treatment were noted by observing the change in size of heart, aorta and/or aortic aneurysm radiologically.

With no treatment, increase in dilatation of the heart, aorta and/or aortic aneurysm was observed radiologically in 52.6% of cases under study. A similar or even less favorable situation exists when patients have received treatment with bismuth and/or arsenic compounds.

Penicillin therapy, either with or without previous bismuth preparation, proved more effective. Only 28.5% of the cases studied showed radiologic evidence of enlargement of the heart or aorta, or aortic aneurysm.

Effects of digitalization were not taken into account, and some portion of the benefit observed following treatment may have been due to proper digitalization.

An effort was made to link actual syphilitic lesions found at autopsy—"tree barking," ulceration and dilatation of the aorta, coronary ostial stenosis, and histologic findings—with antisyphilitic treatment. No instances of acute inflammatory reaction were noted in the syphilitic lesions. Aside from this finding, influence of any type of antisyphilitic therapy on lesions present at autopsy is not apparent.

AUTOPSY FINDINGS

Five hundred twenty-one of the 954 patients (54.6%) in this study died during the period under study; 411 died from causes which might be direct sequelae of syphilitic involvement of the cardiovascular system.

Principal cause of death was congestive heart failure. Among patients with aortic aneurysm, however, rupture of the aneurysm was the main cause of death.

Average age at time of death for all patients was 62.3 years. Mean ages at death for men and women, white and colored, agree with statistics of other investigators,¹⁴ who have found that women have a longer life expectancy than men, and that white persons live longer than do colored ones. The average number of months lived following diagnosis of cardiovascular syphilis—27—also is more or less in accord with findings of other investigators.¹⁵

Autopsies were performed on 275 patients. Average weight of the heart was found to be 506 gm. in males, 429 gm. in females. The smallest hearts belonged to patients with syphilitic aortitis: the largest, to patients with aortic insufficiency.

Coronary ostial stenosis was found in 83 cases (30.2%), which agrees with data cited by other authors.¹⁶ Both ostia were narrowed in 22.2% of cases, the right ostium alone in 6.9%, the left ostium alone in 1.1%. In almost every case of severe stenosis, narrowing of both ostia was present. Eighty-three per cent of coronary ostial stenosis was found in the men; only 17% was found in the women. Patients with aortic insufficiency are most

likely to be affected. Colored persons—women especially—have less tendency to develop coronary stenosis.

Angina pectoris or precordial chest pain was reported in 24.7% of the patients autopsied. Forty-two and seven tenths per cent of patients with typical anginal pain were found to have had coronary ostial stenosis. Conversely, of 83 patients with coronary ostial stenosis, only 29 (35%) had reported precordial pain. Decrease in the percentage of patients reporting precordial pain as one goes from mild to severe stenosis of the coronary arteries may be due to development of functioning collaterals, such as thebesian veins, arteriololuminal channels and intercoronary communications.

A comparison was made between electrocardiographic patterns indicative of coronary insufficiency and the presence or absence of coronary ostial stenosis, and/or angina pectoris. Positive electrocardiographic findings—patterns of anoxia, old and recent infarction and possible infarction—were present in 24.3% of cases with autopsy evidence of stenosed coronary ostia, in 31.6% of cases of angina pectoris or precordial pain, and in 47.6% of cases of coronary ostial stenosis associated with angina pectoris.

PROGNOSIS

Eighty-four and four tenths per cent of patients with cardiovascular syphilis died in the first five years after diagnosis. An additional 10% died in the next five year period. If undiagnosed cases of syphilitic aortitis are included in the tally, persons with aortic insufficiency make up the group of patients most likely to survive the first five years following diagnosis. Naturally, the patient's age at the time of diagnosis is a factor in survival. During the first five years after diagnosis, not much difference is apparent in mortality of persons who were under 59 at the time the diagnosis was established, the incidence of deaths being roughly 30%. Over 60, this percentage increases with increasing age. In the next five year period after diagnosis, however, practically none in the age group under 39 at the time of diagnosis died from cardiovascular syphilis; but 7% of persons in the 40-to-49 year category at the time cardiovascular syphilis is diagnosed die in that interval, and 14% of persons in the 50-to-59 year category die between the fifth and tenth years following diagnosis.

Hypertension influenced prognosis unfavorably, decreasing the period of survival following diagnosis of cardiovascular syphilis to 2.4 months under the average for the group. Complication of true, diastolic hypertension with syphilitic aortic aneurysm was very unfavorable: 77% of these patients died during the period under study. In 47% of these cases, cause of death was a ruptured or dissecting aneurysm.

Angina pectoris caused an increase in death rate of 6% above the rate for the group as a whole.

COMMENT

The striking drop in incidence of cardiovascular syphilis—almost 50% in eight years—may be attributed to widespread information and public education about venereal diseases, and to improved early diagnosis and adequate early treatment of syphilitic infection.³ Persons who sought treatment for cardiovascular syphilis seven to 10 years ago, at the beginning of the period of this study, received their initial infections at about the time of World War I, when Neosalvarsan (first introduced in 1912) was new and untried in the treatment of syphilitic infection, and bismuth compounds (first used in 1921)¹⁷ had recently appeared on the therapeutic scene. Now, with the addition of penicillin to our armamentarium of antisyphilitic drugs, and with good physician-patient coöperation in finding and treating cases of early syphilis, cardiovascular syphilis should become increasingly rare.

The high incidence of positive serologic reactions in cases of cardiovascular syphilis (over 80% in cases in this study) makes everyone with positive serology a candidate for cardiologic examination and adequate treatment with penicillin. False-positives can be excluded by use of the treponema-immobilization test.

Treatment of cardiovascular syphilis was found most effective if given prophylactically, i.e., in the form of early and adequate treatment of early syphilis. In cases receiving early treatment, the life expectancy is over 100% improved as compared with untreated cases.

Evaluation of penicillin therapy in established lesions of the cardiovascular system is difficult because investigators remain undecided as to when treatment has reached its full effect. However, as attempts to produce a penicillin-resistant strain of *Treponema pallidum* have failed,¹⁸ and evidence of true resistance of *Treponema pallidum* to penicillin has not been established,¹⁹ adequate treatment should be effective. Some authors¹² speculate that the disappearance of syphilitic granulomatous tissue from the aorta is a matter of months and perhaps years, and that little if anything happens to the lesions during actual treatment. Nevertheless, observations at autopsy have shown a decrease in lymphocytic and plasma cell infiltration of the aortic wall in cases of aortitis where penicillin treatment was given at least 10 weeks before death.¹¹ Probably another 10 weeks or more are needed for healing to become complete and for penicillin therapy to reach its full effect. This period may vary somewhat, depending upon the extent of the lesions and the amount of granulation tissue present, and may possibly be somewhat longer in more advanced cases.⁴ Perhaps differences in regenerative powers of persons in various age groups are involved.

The death rate from cardiovascular syphilis in the United States underwent a 22% reduction in the years between 1939 and 1948.²⁰ Nevertheless, at least 35% of the patients in this study died from sequelae of syphilitic cardiovascular lesions in the first five years after cardiovascular syphilis was diagnosed.

SUMMARY

1. Charts of 954 patients with cardiovascular syphilis were analyzed to determine trends in incidence, diagnosis, treatment and prognosis at the Los Angeles County Hospital during the years 1945 to 1954.

2. In that period, the incidence of cardiovascular syphilis decreased approximately 47%.

3. Twenty-six and eight tenths per cent of the patients were found to have syphilitic aortitis; 49.5%, syphilitic aortic insufficiency; 9.3%, syphilitic aortic insufficiency associated with syphilitic aortic aneurysm; 14.0%, syphilitic aortic aneurysm.

4. The most common complication was congestive heart failure, followed by hypertension and angina pectoris.

5. Blood serologic reactions for syphilis were positive or repeatedly doubtful in 82% of all patients studied.

6. Radiologic findings were normal in only 8.8% of 633 patients examined.

7. Normal electrocardiograms were obtained in less than 4% of patients examined. No electrocardiographic pattern pathognomonic of cardiovascular syphilis was noted.

8. Penicillin was confirmed as the drug of choice for the treatment of cardiovascular syphilis; progression of cardiovascular lesions was halted (as evidenced by radiologic examination), and untoward reactions were less frequent than were reactions following adequate treatment with bismuth and/or arsenic compounds.

9. Prognosis as to long-time survival was best in the younger age groups.

SUMMARIO IN INTERLINGUA

Malgrado le regression de su incidentia (amontante a 47% in le 10 annos de iste studio), syphilis cardiovascular remane un serie menacia pro le vita e sanitate de su victimas. Inter le 954 patientes con syphilis cardiovascular tractate al Hospital del Contato de Los Angeles durante le annos 1945 a 1954, 26,8% habeva aortitis syphilitic, 49,5% habeva syphilitic insufficientia aortic, 14% habeva syphilitic aneurysma aortic, e 9,3% habeva syphilitic insufficientia aortic associate con syphilitic aneurysma aortic. Le plus commun complicationes esseva congestive disfallimento cardiac, hypertension, e angina de pectore. Positive o repetitemente dubitose reactiones serologic occurreva in 82% de omne patientes studiate. Normal constatationes radiologic esseva facite in solmente 8,8% del patientes assi studiate. Ben que nulle constatationes electrocardiographic esseva facite que poteva esser considerate como pathognomonic pro syphilis cardiovascular, le electrocardiogrammas obtenite esseva normal in minus que 4% del casos. Le prognose de prolongate periodos de superviventia esseva le plus favorable pro patientes de gruppos de etate plus juvene. Esseva confirmate que penicillina es le droga de election in le tractamento de syphilis cardiovascular.

BIBLIOGRAPHY

1. Bauer, T. J.: Public health problems in syphilis control, J. A. M. A. 152: 300, 1953.
2. Wright, J. J.: Venereal disease control, J. A. M. A. 147: 1408, 1951.

3. White, P. D.: Changes in relative prevalence of various types of heart disease in New England, *J. A. M. A.* **152**: 303, 1953.
4. Anderson, W. A. D.: Pathology, 2nd Ed., 1953, The C. V. Mosby Company, St. Louis, p. 459.
5. Stokes, H. H., Beerman, H., and Ingraham, N. R.: Modern clinical syphilology, 1945, W. B. Saunders Co., Philadelphia, pp. 893-966.
6. Beerman, H.: Penicillin treatment of cardiovascular syphilis, *Am. J. M. Sc.* **224**: 447, 1952.
7. (a) Lucia, S. P., Harp, V. C., and Hunt, M. L.: Cardiovascular syphilis in a general medical clinic, *Pub. Health Rep.* **63**: 405, 1953.
7. (b) Thorner, M. C., Carter, R. A., and Griffith, G. C.: Calcification as a diagnostic sign of syphilitic aortitis, *Am. Heart J.* **38**: 641-653 (Nov.) 1949.
8. Kampmeier, R. H., and Morgan, H. J.: The specific treatment of syphilitic aortitis, *Circulation* **5**: 771, 1952.
9. Edeiken, J., Ford, W. T., Falk, M. S., and Stokes, H. J.: Further observations on penicillin treated cardiovascular syphilis, *Circulation* **6**: 267, 1952.
10. Krantz, W.: Ist die Syphilis heilbar? *Dermat. Wchnschr.* **125**: 82, 1952.
11. Sinclair, H. A., and Bruce, W.: The effects of penicillin treatment on the microscopic appearance of syphilitic aortitis, *Am. J. Syph., Gonorr. and Ven. Dis.* **38**: 54, 1954.
12. Bruetsch, W. L.: Penicillin therapy of cardiovascular syphilis with large total dosage, *Am. J. Syph., Gonorr. and Ven. Dis.* **35**: 252, 1951.
13. Morton, H. E., and Ford, W. T.: Preliminary observations on the action of penicillin on *Treponema pallidum* in vivo, *Am. J. Syph., Gonorr. and Ven. Dis.* **37**: 529, 1953.
14. Webster, B., Rich, C., Jr., Densen, P. M., Moore, J. E., Nicol, C. S., and Pedget, P.: Studies in cardiovascular syphilis. III. The natural history of syphilitic aortic insufficiency, *Am. Heart J.* **46**: 117, 1953.
15. Montgomery, B. M., Anderson, R. M., and Boone, J. A.: The natural history of syphilitic heart disease, *Ann. Int. Med.* **37**: 689, 1952.
16. Gould, S. E.: Pathology of the heart, 1953, C. C. Thomas, Springfield, Illinois, p. 764.
17. Rencis, Ed.: Farmakologija, University Press, Riga, 1942, pp. 236 and 181.
18. Morgan, H. J., and Kampmeier, R. H.: Syphilitic heart disease, *Heart Bull.* **1**: 92, 1952; **2**: 2, 1953.
19. Beerman, H., Nichols, L., Buerk, M. S., and Ford, M. T.: Syphilis: a review of the literature, *Arch. Int. Med.* **85**: 305, 1950.
20. Usilton, L. J., Remein, Q. R., Thorner, R. M., and Donohue, J. F.: Syphilis mortality during the period of the fifth revision of the international lists of causes of death, *Am. J. Syph., Gonorr. and Ven. Dis.* **37**: 403, 1953.

THE NATURAL HISTORY OF CEREBRAL THROMBOSIS *

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DURING the last 10 years the profession and public alike have become more and more concerned about the increasing extent of morbidity from cerebrovascular disease.

In 1955 serious concern was expressed by Wright¹ about the social implications of invalidism resulting from this disorder. As far back as 1888 Gowers² had listed in his textbook of medicine some of the problems in relationship to morbidity and recovery which were significant in the management of this disease. One of the major difficulties in evaluating new modes of management has been the lack of adequate knowledge of the natural course of the condition, and Millikan¹ in 1954 made an earnest plea for long-term studies on this problem so that an adequate control group might be established with which to compare the results of treatment methods. The literature has been flooded with suggested procedures, ranging from major neurosurgical attacks to various types of drugs. Most of these have been summarized by Sheldon,³ but none can be thoroughly evaluated, as the controls are either nonexistent or inadequate; and the cases have not been followed for sufficient time.

This communication is written in an effort to fill partially this gap in our knowledge, and is a report on a study of 117 patients admitted to Deer Lodge Hospital between January 1, 1948, and December 31, 1949, all suffering from acute cerebral thrombosis. These were all male patients, varying in age, as noted in table 1, with the predominant age between 50 and 80 years.

TABLE 1
Age by Decades

Years:	
20-30.....	1
30-40.....	5
40-50.....	5
50-60.....	26
60-70.....	44
70-80.....	30
80-.....	5

The criteria for diagnosis of thrombosis were: the usual clinical history; evidence of hemiparesis on one or the other side; absence of blood in the spinal fluid; no evidence radiologically of pineal shift, and no evidence of

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severe intracranial pressure; recovery of consciousness within a period of 48 to 72 hours after admission.

Seventy of these cases were hypertensive, the criterion for this being a level of 160 systolic and 90 diastolic as the normal range for age. All cases were admitted to one ward, and a standard treatment method was utilized, consisting of early ambulation, physiotherapy, good nursing management, and supportive treatments as outlined by Covalt,⁴ Dinken⁵ and Twitchell.⁶ No special management was given such as stellate block, anticoagulant therapy, antispasmodic treatments, tranquilizing drugs or other forms of specialized treatment. The hospitalization period lasted from six weeks to three months, and a functional evaluation was made at the time of admission, at the time of discharge, in 1952 and in 1956. The method of evaluation used is a modification of the functional assessments described by Dinken,⁵ in which the functional capacity is represented in figures from 0 to 5—"0" represents complete loss of function, and "5" represents normal function. Three major aspects—arm function, leg function and speech—were assessed, as it was found that these were most readily documented and were most indicative of the degree of disability. The results of this survey follow.

MORTALITY

Sixteen patients died in the initial hospital period of the cerebrovascular accident or of complications resulting therefrom. The remaining 101 patients were discharged from hospital, and of this group 55 had died by 1956. Table 2 shows the year of death, and table 3 the causes of death. All but

TABLE 2
Death by Years

	1949	1950	1951	1952	1953	1954	1955
No. of Patients	4	14	7	11	9	4	6

four cases had postmortem examinations and the cause of death was verified. Three in whom post mortem was not obtained have been listed as "unknown," and one other had classic myocardial infarction shown by electrocardiogram, and died in cardiac failure, although autopsy was refused.

The number of deaths must be related to the life expectancy of this particular age group. Although the comparison between these and presently

TABLE 3
Causes of Death

	Cerebro-vascular	Cardiac	Malignancy	Respiratory Infection	Others	Unknown
No. of Patients	12	21	7	6	6	3

existing life insurance tables is not valid because of the selection of the group, it is interesting to note that approximately the same number of deaths would have occurred in a normal population with an average age of 63 years. This group has an average age of 63.5 years. According to the Canadian Sickness Surveys,⁷ the incidence of mortality and morbidity should have been approximately 65% of this age group, and this, perhaps, is of significance as a comparative figure.

As to the causes of death, it is interesting to notice the high preponderance of cardiac deaths, most of these resulting from arteriosclerotic heart disease. The incidence of cerebrovascular death is actually lower than one would expect from the normal population, as noted in the Canadian Sickness Survey,⁷ where 18% of this age group should die of cerebrovascular disorders. It is recognized, however, that these figures must stand by themselves, and do not lend themselves to comparison with the general population because of the pre-selection of the group due to previous Army service, its all-male character, etc. However, there was a sufficient variation in such factors as social setting, economic situation, occupations and activities. Surprisingly few cases had cerebrovascular deaths, though it is the general opinion that recurrence and death in a short period of time are the likely result from a cerebrovascular accident. With only 12 of 101 patients dying of this cause in an eight year period, the suggestion is made that recurrence and death from this cause are not the usual sequence, and that it would be of value if the program of therapy were regularly based on a more optimistic outlook as to the outcome of the initial episode.

More interesting than the deaths, however, were the number of recurrences in the group who died. There were 21 recurrences, occurring in 16 patients, giving a recurrence rate in the group of deaths of 30%.

MORBIDITY

In spite of the fact of their death, the functional capacity of this group is interesting to note if one compares the figures in the discharge column of tables 4, 5 and 6, which shows that the number of cases improved to a good functional capacity is surprisingly high. Even though their survival was less than eight years, these people remained less of an economic and social burden and were without doubt happier and more content than would normally be expected following a severe cerebral episode.

TABLE 4
Disabilities of Arm

	0	1	2	3	4	5
Initial	21	6	13	19	4	1
Discharge	0	4	6	17	19	18
1952	0	2	6	14	21	19
1956	0	0	4	11	12	12

TABLE 5
Disabilities of Leg

	0	1	2	3	4	5
Initial	17	4	15	14	10	4
Discharge	0	0	4	16	22	21
1952	0	0	3	3	21	26
1956	0	0	1	9	18	11

Of particular interest were the 46 survivors, who were reviewed at the end of the eight year period. Thirty-nine of these cases have been followed carefully; the remaining seven have been lost or have moved to other centers where an adequate appraisal is not possible. The functional status of this group in both 1952 and 1956 indicates an extremely high degree of return of function which has been maintained over the long-term period. It must be recognized that the majority of these people are now eight years older, and the average age at this point of assessment in 1956 has risen considerably—66 years for the survivors. Therefore, gainful employment is not the expected activity of this group. Social function, therefore, was determined

TABLE 6
Disabilities of Speech

	0	1	2	3	4	5
Initial	12	10	4	8	5	24
Discharge	0	2	8	8	11	35
1952	0	1	4	13	10	34
1956	1	1	3	9	6	19

on the basis of: (1) those who were at home and functioning adequately for their years; (2) those who were at home and who required supervision and/or nursing care, and (3) those who were confined to institutions. Table 7 follows.

TABLE 7
Social Function

	Home and Functioning	Home and Nursing Care	Institutions
No. of Patients	24	5	10

In this group of survivors, out of 39 cases only four had suffered recurrences, which is less than 10%. This leads us to suspect that in those cases where recurrence is present, mortality is increased, and they are much less likely to survive for a long-term period or to make a good eventual functional recovery.

With these figures as a background, it would seem possible to divide the group of cerebral thromboses into two specific subgroups, which might

require different management in the long-term view. First are those with recurrence, in whom the mortality and morbidity seem excessively high in comparison with the second group, in whom recurrence is infrequent and functional recovery seems adequate. The maintenance of the recovery over the long period is an important encouragement to those people who are engaged in extensive programs of rehabilitation for this type of patient, as it indicates that improvement, once obtained, is not transient, nor is there evidence of a senile deterioration to a point where this treatment is of little value. The surprising figure of 24 out of 117 cases who are functioning adequately at the end of eight years indicates the necessity of more worthwhile therapy and attention being given to these cases in the initial phase. If this figure can be improved upon by other modes of therapy, then it is apparent that some specific stride has been made in solving the serious problem of economic and institutional difficulties resulting from this disorder.

SUMMARY

A series of 117 cases of cerebral thrombosis has been tabulated and analyzed at the end of an eight year period following their initial episode. The results have been discussed and presented in order that some base-line can be established upon which to gauge the values of new modes of treatment.

SUMMARIO IN INTERLINGUA

Iste communication concerne un studio de 117 patientes de thrombosis cerebral qui esseva tractate al Hospital Deer Lodge inter le 1 de januario 1948 e le 31 de decembre 1949.

Omne le casos esseva admittite al mesme departimento, e un methodo standard de tractamento con ambulation precoce, physiotherapia, e bon sollicitude clinic esseva utilisate. Nulle forma specialisate de tractamento es includite in le serie. Le periodo de hospitalisation durava inter sex septimanas e tres menses. Evalutationes del nivellos functional esseva effectuate al tempore del admission, al tempore del dimission, e in 1952 e 1956. Le tres aspectos principal includite in le evalutation esseva function de bracio, function de gamba, e function de parlar, proque il habeva essite constatate que istos esseva le plus fidel indices del grado de invaliditate.

Dece-sex patientes moriva durante le hospitalisation initial. Ex le remanente 101, 55 moriva ante 1956. Le causas de morte es citate insimul con le correspondente numeros. Un comparison del mortalitate inter iste patientes con tabulas de as-securantia vital indica que le mesme numero de mortes haberea occurrite in un population normal con un etate medie de 63 annos.

Un surprendentemente basse numero de mortes occurreva in consequentia de conditiones cerebrovascular. Solmente 12 del 101 patientes original moriva ab iste causa. Vinti-un patientes habeva attaccos cerebrovascular recurrente, sed le melioration post le attacco initial esseva exceptionalmente marcate, mesmo inter le patientes qui non superviveva.

Un revista de 46 superviventes al fin del periodo de octo annos indicava que un alte grado de retorno de function habeva essite mantenite. Un analyse del function social de 39 patientes indicava que 24 fungeva adequatemente in lor domicilios, 10

esseva in institutiones, e solamente cinque requireva surveillantia e/o attention de infirmas.

Il pare possibile divider le gruppo in duo subgrupos a tractamento possibilmente differente. Le prime gruppo include patientes con recurrentias. Inter illes le grados de mortalitate e de morbiditate es apparentemente alte. Le secunde gruppo include le patientes in qui recurrentias occurre infrequentemente e in qui le restablimento functional es bon.

Le mantenentia del stato de restablimento durante un si longe periodo es importante como incoraggiamento pro individuos qui participa in extense programmas de rehabilitation pro iste typo de patiente. Illo indica que quando on ha attingite un melioration in le stato del patiente, iste melioration non es de character transiente. Il etiam ha nulle evidentia del occurrentia de deterioration senil a grados ubi le tractamento perderea un grande parte de su valor.

Es exprime le spero que iste studio pote servir como base de referentia in le evaluation de altere modos therapeutic.

BIBLIOGRAPHY

1. Wright, I. S., and Luckey, H. E.: Cerebral vascular diseases, 1955, Grune & Stratton, Philadelphia.
2. Gowers, W. R.: Manual of diseases of the nervous system, 1888, J. & A. Churchill, London.
3. Sheldon, K. W.: Management of strokes, 1956, Lippincott & Company, Philadelphia.
4. Covalt, D. A.: Rehabilitation of the patient with hemiplegia, *Ann. Int. Med.* 37: 940, 1952.
5. Dinken, H.: Evaluation of disability and treatment in hemiplegia, *Arch. Phys. Med.* 28: 263, 1947.
6. Twitchell, T. E.: Restoration of motor function following hemiplegia, *Brain* 74: 443, 1951.
7. Charron, K. C.: Report to Canadian Conference on Rehabilitation, Ottawa, 1955.
8. Adams, G. F., and McComb, S. G.: Assessment and prognosis in hemiplegia, *Lancet* 2: 266 (Aug. 8) 1953.
9. Brain, W. R.: Disease of the nervous system, 1951, Oxford University Press, New York.
10. Cecil, R. L., and Loeb, R. F.: Textbook of medicine, 1947, W. B. Saunders Company, Philadelphia.
11. Warren, M.: Retraining the elderly hemiplegic, *Geriatrics* 8: 198, 1953.
12. Millikan, C. H., and Moersch, F. P.: Factors that influence prognosis in acute focal cerebrovascular lesions, *Arch. Neurol. and Psychiat.* 70: 558, 1953.
13. Feldman, L.: Positive approach to management of cerebrovascular accidents, *Geriatrics* 6: 214, 1951.

AMYLOIDOSIS: ITS CLINICAL AND PATHOLOGIC MANIFESTATIONS, WITH A REPORT OF 12 CASES *

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AMYLOIDOSIS is a generalized disease characterized by the deposition of a homogeneous substance in the media of arteries and perivascular connective tissues. Because of its starchlike staining with iodine, Virchow (1853) considered the substance a carbohydrate moiety, and originated the term "amyloid." The chemical nature of amyloid has never been clearly elucidated, but the studies of Eppinger (1922) and Hass (1940)²¹ demonstrated the presence of both protein and polysaccharide elements. It is not known whether the substance is produced locally or transported to the site of deposition, nor is it known whether it is an abnormal substance, or a normal one produced in amounts too great for utilization. Amyloid has been reported in small amounts in the otherwise normal tissues of senile mice and the hearts of aged patients.^{27, 28} Because amyloid can be produced experimentally^{39, 42} by the injection of colloidal sulfur, selenium, sodium caseinate, bacterial toxins, gelatin and egg albumin, the concept of antigen-antibody interaction has been suggested as a factor in pathogenesis.³⁴ Amyloid has also been produced by administering nitrogen mustard. ACTH and cortisone used in conjunction with nitrogen mustard enhance amyloid deposition and delay its reabsorption after mustard therapy has been discontinued.⁴² The known cytotoxic effect of nitrogen mustard, and inhibitory effect on inflammatory reaction of adrenal cortical steroids, suggest "that a suppression of mesenchymal cells which are in a state of active proliferation is involved in the basic mechanism of the formation of amyloid."⁵⁰ Amyloid has been reported in patients with Hodgkin's disease^{28, 57} who have been repeatedly treated with nitrogen mustard and who have had unusually long survivals. Amyloid deposition occurs in 15% of cases of multiple myeloma;⁸ this has directed speculation as to the rôle of a hyper- or abnormal globulinemic state²⁴ in the pathogenesis of amyloid. Because of the occurrence of amyloid in connective tissue diseases, it has been suggested that amyloid is another collagen disease.³²

The disease has been divided into primary and secondary categories on the basis of: (1) presence or absence of inciting disease, (2) distribution of involvement, and (3) the staining reaction. Primary amyloidosis occurs without preëxisting disease and has widespread organ involvement. It

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almost invariably involves the heart,^{1, 9} and in two thirds of cases spares the liver, kidney, spleen and adrenal. The heart is rarely involved in the secondary form, and the parenchymal organs (liver, spleen, adrenal, kidney) are invariably involved.⁵⁰ The secondary form of amyloid has a constant affinity for certain dyes (Congo red, crystal violet, methyl violet), but the staining of primary amyloid is not predictable. Since there is no known chemical dissimilarity between primary and secondary amyloid, and since there is considerable overlap of organ involvement in the two forms, criticism has been directed at the clinical separation.⁹

By 1950 only 70 cases of primary amyloidosis had been reported.²² In the last five years 30 additional cases have been added.³² It is probable that the disease is being suspected more frequently, rather than that there has been a true increase in the number of cases. Of the 70 cases previously reported, in only 14 was the diagnosis made ante mortem.^{1, 22} Secondary amyloidosis is common in autopsy series; the incidence has been reported to be as high as 24% with tuberculosis and 20% with rheumatoid arthritis.^{6, 17, 40, 49, 53} The frequency in tuberculosis accounts for 80 to 90% of reported cases of secondary amyloidosis. Amyloidosis has also been seen in association with osteomyelitis, bronchiectasis, empyema, actinomycosis, ulcerative colitis, syphilis, subacute bacterial endocarditis, chronic urinary tract infection, carcinoma, lymphoma and leukemia. The incidence is higher where a chronic fistula or sinus tract exists.

Amyloid tumors⁴⁶ represent local accretions of amyloid tissue; they are found most frequently in the respiratory tract, but have also been reported involving the eye, urinary tract and central nervous system. These lesions are generally localized and benign, but systemic amyloidosis has appeared after the excision of an amyloid tumor.

Amyloid disease presents itself clinically with a variety of manifestations, which may occur singly or in combination, depending on the extent and severity of the process. Heart failure is responsible for the death of 50% of those with primary amyloidosis.^{1, 6, 7, 9} A 70% incidence of renal failure has been reported in those dying of secondary amyloidosis.^{6, 80} Liver failure with jaundice,^{4, 45, 47, 52, 58} gastrointestinal hemorrhage,^{4, 15, 58} adrenal cortical insufficiency^{5, 6, 33, 39} and a spruelike syndrome¹⁵ have also been reported in amyloid disease.

The rate of accretion of amyloid is unpredictable. It may be fairly rapid. Tissues have been examined and found free of amyloid within a few months of clinical onset of the disease, with death resulting within two years. It is said that primary amyloidosis is a more slowly progressive disease than the secondary form. This has been used as an explanation for the difference in staining reaction. We know of no statistics that would indicate that the secondary form is more fulminant.

The diagnosis of the disease rests on Congo red absorption and biopsy. Bennhold (1922) originally observed that Congo red was absorbed by

amyloid tissue, and established the figure of 60% loss of Congo red to the tissues between a four and a 60 minute specimen as the requirement for a positive test. Selikoff⁴³ suggests that the criteria for the diagnosis be made more rigid to exclude false-positives. He would require 90 to 100% removal on two consecutive tests for a positive diagnosis. Unger et al.⁵⁴ suggest a method to obviate the inadequacies of the original method. A two or four minute specimen (the 100% figure) does not allow adequate mixing, nor does it measure dye being lost to amyloid tissue during this time. They suggest serial determinations. From these a curve is constructed and a more nearly accurate initial level (100% figure) is obtained by extrapolation back along the curve to the time of injection. Congo red remains in amyloid tissue for at least several days, as witnessed at necropsy.¹⁸ The skin similarly may retain Congo red, and caution has been advised in administering the dye when the skin is known to be involved. Congo red can probably saturate amyloid tissue so that repeated testing within short periods may give conflicting results. The tongue and gingiva are involved sufficiently often in the primary disease that biopsy should be done in suspected cases. Selikoff⁴⁴ claims that in secondary amyloidosis gingival biopsy may be equally rewarding. Biopsy may be the only way of establishing the diagnosis in primary amyloidosis when Congo red is not retained. Liver biopsy has been performed frequently to establish the diagnosis. Because an amyloid organ is friable and cannot be readily repaired surgically, caution should be observed in performing aspiration biopsy when amyloid is suspected. Volwiler and Jones⁵⁵ report a death from hepatic hemorrhage following biopsy. The spontaneous rupture of amyloid spleens has also been reported.^{12, 20}

CASE REPORTS

For purposes of discussion the cases have been arranged according to their predominant manifestations. The first case compounds the phenomena observed in succeeding cases, and is discussed separately.

Case 1. Renal failure—adrenal cortical failure—hemorrhage. A 26 year old white male was found to have Hodgkin's disease by lymph node biopsy in 1945. From 1948 to 1954, during 22 hospitalizations, he received 780 mg. of nitrogen mustard, 185 mg. of triethylene melamine (TEM) and x-ray therapy to the left axilla, spleen and mediastinum. During his early admissions the urine was acid, concentrated well (1.023), and contained no albumin. The liver and spleen became enlarged in 1948. In 1950 albuminuria appeared and persisted. In 1952 polyuria appeared, and the urine did not concentrate beyond 1.012. Congo red was 90% retained by the tissues. In 1953 nonprotein nitrogen elevation (53 mg.%) was first noted. The urine was then alkaline and remained so thereafter. Albuminuria (9.7 gm. in 24 hours) and albuminemia (2.4 gm.%) were present. Alkaline phosphatase was elevated to 20 Bodansky units. In October, 1953, epistaxis, anorexia, diarrhea, abdominal pain, dyspnea, and pain and tingling in the legs developed. Deep and rapid respirations were present. Increased skin pigmentation was noted. No pulses could be felt in the lower extremities. CO_2 combining power was 5 m. mol/L;

chloride, 90 mEq./L.; sodium, 141 mEq./L.; potassium, 4.3 mEq./L. Nonprotein nitrogen was 137 mg.%. In addition to large amounts of saline, the patient received 788 mEq. of sodium lactate during the first five days. Respirations improved but the CO_2 combining power remained very low (7.5 m. mol/L.). Despite his marked acidosis the urine remained alkaline. One 24 hour urine specimen contained 134 mEq. of sodium and 194 mEq. of potassium. He excreted 2,000 to 2,500 c.c. urine per day.

Diarrhea and anorexia continued after admission, and on the third hospital day hypotension (80/40 mm. of Hg) developed. He was thought to have adrenal cortical insufficiency secondary to amyloid involvement. He received cortisone thereafter, in doses varying from 25 to 150 mg. per day, and improved. In November, 1953, by which time cortisone had been reduced to 25 mg. per day, a minor surgical procedure (skin biopsy) was performed. Following this he developed a pneumococcal septicemia and went into shock (blood pressure, 40/0 mm. of Hg). He was treated with large doses of penicillin, 60 c.c. of aqueous adrenal extract, 20 mg. of DOCA, and 200 mg. of cortisone. His blood pressure rose to 115/70 mm. of Hg, and after 19 hours of anuria he again produced urine.

In early January, 1954, massive gastrointestinal hemorrhage occurred and the patient died.

Postmortem examination revealed extensive amyloid involvement of kidney, adrenal and liver, with lesser involvement of lymph nodes and spleen. There was focal deposition of amyloid in the arterioles of pancreas, prostate, and gastrointestinal tract. The villi of the small bowel contained amyloid. The gastrointestinal tract was filled with blood. Hodgkin's disease was not found.

Comment: This case showed evidence of renal, adrenal, gastrointestinal and vascular involvement with amyloid. The underlying disease had been present nine years. The patient had received a large total dose of mustard. At necropsy there was no evidence of Hodgkin's disease, despite earlier biopsy diagnosis and repeated satisfactory responses to nitrogen mustard and x-ray therapy. In the absence of significant Hodgkin's disease, at any rate, the renal, adrenal, gastrointestinal and hemorrhagic manifestations can be attributed to amyloidosis only.

Case 2. Renal failure. In April, 1945, a 29 year old white male was paralyzed below D-10. He developed osteomyelitis of the right hip with a draining sinus. In November, 1950, liver enlargement was first noted. Prior to 1950 the urine had been albumin-free, concentrated well, and was usually acid. By mid-1950 the urine failed to concentrate beyond 1.010, contained albumin, and was persistently alkaline. Amyloidosis was suspected, and Congo red was 85% retained by the tissue. In November, 1953, the patient developed fever, nausea, vomiting, pericardial friction rub, and edema of the lower extremities. A generalized convulsion occurred. He had a positive Chvostek's sign, nonprotein nitrogen was 55 mg.%; CO_2 combining power, 4.7 m. mol/L.; chloride, 100 mEq./L.; sodium, 134 mEq./L.; potassium, 4.3 mEq./L.; calcium, 6.4 mg.%; inorganic phosphorus, 9.9 mg.%. The white blood cell count was 24,500, and a beta-hemolytic streptococcus was cultured from the blood. Over a 48 hour period, in addition to antibiotics and calcium gluconate, the patient received 178 mEq. of sodium lactate (calculated to raise the CO_2 combining power 10 m. mol/L.). However, several determinations failed to show significant change in the CO_2 combining power. The urine remained alkaline. The patient developed respiratory irregularity, became comatose, and died during a convulsion.

Postmortem examination revealed extensive amyloidosis of the kidney, with tubular atrophy, and hydropic nephropathy of the remaining tubular cells.

Comment: Renal failure related to amyloidosis and septicemia was the cause of death. There was insufficient evidence clinically or at autopsy to suggest that adrenal cortical insufficiency played a rôle. The nature of the renal failure and associated electrolyte disturbance is essentially a duplicate of case 1.

Case 3. Renal and adrenal cortical failure. In April, 1945, a 23 year old white male was paralyzed below D-3. He developed a chronic draining sinus over the right greater trochanter. The urine was persistently alkaline, contained albumin, and did not concentrate beyond 1.010. Congo red was 66% removed from the serum. Because of the demonstrated focus of chronic infection with evidence of secondary amyloidosis, the sinus tract and the head and neck of the right femur were excised. Preoperatively the nonprotein nitrogen was 53 mg.%; CO₂ combining power, 24 m. mol/L.; and chloride, 94 mEq./L. On the eighth hospital day, spasm of the lower abdominal muscles occurred. At that time the patient was hypotensive (55/40 mm. of Hg) and had a positive Chvostek's sign. The nonprotein nitrogen was 52 mg.%; CO₂ combining power, 8.5 m. mol/L.; chloride, 107 mEq./L. Inorganic phosphorus was 12 mg.%; creatinine, 13 mg.%. Calcium was 6.0 mg.%. The urine contained 7.5 gm. albumin (24 hour specimen) and was alkaline. The patient was considered to have amyloid involvement of the kidneys and adrenals, and was treated with 100 mg. of cortisone daily, intravenous saline and calcium gluconate. He responded with a rise of blood pressure 110/80 mm. of Hg. The nonprotein nitrogen stabilized in the range of 70 to 80 mg.%. The CO₂ combining power remained between 9 and 11 m. mol/L. An attempt at dialysis on the artificial kidney had to be interrupted because of blood clotting. In April, 1954, three days after omission of cortisone, the patient was found to be hypotensive and semi-comatose. The nonprotein nitrogen was 69 mg.%; CO₂ combining power, 12 m. mol/L.; chloride, 79 mEq./L.; sodium, 122 mEq./L.; potassium, 3.5 mEq./L.; calcium, 6.5 mg.%; inorganic phosphorus, 12 mg.%. He was treated with 30 c.c. of aqueous adrenal extract initially, and over the next 72 hours received 920 mEq. of sodium, 140 mEq. of potassium, and 1,060 mEq. of chloride. He was also given 200 mg. of cortisone and 5 mg. of DOCA daily. He responded initially, with chlorides rising to 104 mEq./L., sodium to 136 mEq./L. and blood pressure to 100/60 mm. of Hg. However, about two weeks later he developed an otitis media and bronchopneumonia, became increasingly dyspneic and cyanotic, and died on May 24, 1954.

At necropsy the liver, kidney, adrenal cortex and spleen were extensively involved with amyloid, with lesser involvement of the arterioles of the pancreas, gastrointestinal tract, prostate and testes. There was amyloid deposition in the villi of the ileum. There was a recent thrombosis of the right adrenal vein with associated cortical necrosis (weight, less than 1 gm.).

Comment: In this patient, renal and adrenal cortical failure occurred postoperatively. Adrenal insufficiency was initially controlled, but renal insufficiency persisted, with manifestations indistinguishable from those of the preceding cases. The terminal episode of adrenal cortical insufficiency was precipitated by infection, cortisone withdrawal and adrenal cortical necrosis.

Case 4. Renal and probable adrenal cortical failure. On the basis of nystagmus, dorsal column and pyramidal tract signs in a 51 year old white male, the diagnosis of multiple sclerosis was made in 1948. Nine months later he developed ankle edema, nocturia, a greatly enlarged liver, clubbing and plethora. The hematocrit was 62%.

The urine failed to concentrate beyond 1.011 and contained 4 plus albumin. Non-protein nitrogen was 61 mg.%. Total cholesterol was 357 mg.%. Bromsulphalein was 32% retained after 45 minutes. The alkaline phosphatase was 40.8 Bodansky units. Liver biopsy showed amyloid. The edema increased, ascites appeared and diarrhea developed. Serum albumin fell to 1.6 gm.%. Cholesterol rose to 604 mg.%. The nonprotein nitrogen rose to 147 mg.%, calcium fell to 7.6 mg.%, CO₂ combining power to 13.5 m. mol/L. In early December, 1949, a low blood pressure (80/50 mm. of Hg) was noted. In the succeeding two weeks the patient became weaker, and on December 17, 1949, he died.

Necropsy showed marked deposition of atypically staining amyloid in the renal glomeruli, and extensive tubular necrosis with hyaline droplet deposition in much of the remaining tubular epithelium. The adrenals were extensively infiltrated with amyloid. The pancreas was involved to a lesser degree. The heart, tongue, bone marrow and muscles were free of amyloid.

Comment: This case, by virtue of the distribution of the amyloid, would fall into the secondary category and be related to multiple sclerosis. To our knowledge, such relationship has not been reported. The amyloid stained atypically suggesting the primary disease. This emphasizes the difficulty of attempting classification. The terminal hypotension, nausea, diarrhea and weakness suggest adrenal cortical hypofunction, but this was not substantiated by laboratory test or by therapeutic trial.

Case 5. Renal and adrenal cortical failure. A 57 year old white male was hospitalized in April, 1947, because of rheumatoid arthritis of 25 years' duration. In November, 1947, a Congo red test showed 80% retention, though there was no clinical evidence to suggest amyloid disease. In November, 1949, albuminuria was first noted. The urine did not then concentrate beyond 1.010, was alkaline, and thereafter remained so. Nonprotein nitrogen was 80 mg.%. In November, 1950, a cataract extraction was done. Following the procedure the patient became drowsy and distended, had repeated vomiting, and became hypotensive and oliguric. The nonprotein nitrogen rose to 160 mg.%; CO₂ combining power, 10 m. mol/L. The patient developed pulmonary edema and, terminally, an *Aerobacter aerogenes* bacteremia. He died on his tenth postoperative day.

At autopsy there was pulmonary edema and evidence of septicemia. There was no evidence of pyelonephritis. The adrenals and, to a lesser extent, kidneys, liver and spleen, were involved with amyloid.

Comment: This case was terminated by renal failure, probably adrenal cortical failure, and septicemia, following a relatively minor surgical procedure. Renal failure was not due to pyelonephritis but was probably related to hypotension, septicemia and amyloid involvement. Considering the degree of amyloid involvement, adrenal cortical failure could well have been a factor in the postoperative course. However, studies were inadequate to substantiate this.

Case 6. Adrenal failure. In 1943 a 23 year old white male developed rheumatoid arthritis. In June, 1950, he received ACTH, with temporary improvement. In November, 1950, albuminuria was first noted. The alkaline phosphatase was elevated to 18 Bodansky units. Amyloid disease was suspected. Congo red was 95% removed from the serum. In January, 1951, cortisone was started and continued

thereafter in doses varying between 50 and 150 mg. per day. The patient was at this time excreting large amounts of albumin (10 to 12 gm. per day), and the serum albumin had fallen to 0.8 gm.%. Serum globulin was elevated (5.4 gm.%). Cephalin flocculation was 4 plus; bromsulphalein was 40% retained after 45 minutes; cholesterol, 509 mg.%; alkaline phosphatase, 14 Bodansky units. In August, 1951, the liver first became palpable. Despite evidence of continuing renal disease, the urine concentrated well (1.020), and nonprotein nitrogen was not elevated. By April, 1952, there was massive hepatomegaly (iliac crest), moon face, girdle obesity, striae, hypertension and glycosuria. In August, 1952, petechiae appeared over the abdomen and upper extremities, though there was no abnormality of bleeding or clotting mechanisms. On October 1, 1952, during his twentieth month of cortisone therapy, the patient developed an exquisitely tender right knee, became febrile, went into shock and died. Both a culture of joint fluid aspirated at onset of symptoms and a blood culture taken just before death grew a pneumococcus Type 23.

At necropsy there was an acute, purulent arthritis of the right knee. There was extensive amyloid involvement of the liver and kidney, and lesser involvement of the spleen and adrenals. The gastric mucosa was minimally infiltrated. The liver was massive and was stained with Congo red (given four days prior to death). The hepatic parenchyma was 90% replaced by amyloid. The adrenals were very small (not more than 1 mm. of cortex), and had minimal amyloid involvement. The kidneys were large and extensively infiltrated with amyloid. There was no evidence of pneumonia.

Comment: Twenty months of cortisone therapy suppressed adrenal cortical function and produced the adrenal atrophy observed pathologically. In the presence of a cortisone-concealed pneumococcal septicemia, additional endogenous cortisone could not be produced, supplementary cortisone was not given, and the patient died, essentially of acute adrenal cortical insufficiency.

Case 7. Hemorrhage (vascular failure). In April, 1945, a 19 year old white male developed urethritis, arthritis and conjunctivitis, and the diagnosis of Reiter's syndrome was made. He remained symptomatic. In August, 1951, ACTH was started and, save for brief trial periods with cortisone and compound F, he remained on either intravenous or intramuscular ACTH for the next three and a half years. The picture of Cushing's disease developed, with obesity, hypertension and osteoporosis. In May, 1952, Congo red was found to be totally retained by the tissues. Except for 45% retention of bromsulphalein after 45 minutes, all liver function studies were normal. In late 1952 the liver became enlarged and albuminuria appeared (2.0 gm. in 24 hours). In January, 1955, a large, spontaneous hemothorax occurred. He then began to lose small amounts of blood through the gastrointestinal tract, and bleeding was noted at the sites of parenteral injection. Investigation of bleeding and clotting mechanisms revealed no abnormality.* Hemorrhage continued and he died.

At necropsy there was evidence of Cushing's disease (iatrogenic), and arthritis. There were 3,000 c.c. of blood in the left chest with a large hematoma at the left hilum. The site of intrathoracic hemorrhage could not be found. The liver was massive and the hepatic parenchyma was considerably replaced with amyloid. The adrenals were huge (28 and 38 gm. respectively), and showed slight amyloid infiltration. The kidneys showed a moderate glomerular involvement and extensive tubular

* The following were done and found normal: bleeding time, clotting time, platelet count, prothrombin time, prothrombin consumption, recalcification time, clot retraction, and fibrinogen level. There was no circulating fibrinolysin.

necrosis. The stomach mucosa was atrophic and largely replaced by amyloid. A focal myocarditis was present, and there was hemorrhage into the papillary muscles, but no amyloid was present in the heart. There were amyloid deposits in the arterioles of the pancreas, and gastrointestinal tract.

Comment: This patient died of exsanguination. With normal clotting mechanism, and evidence of arteriolar involvement with amyloid, it is probable that death was related to hemorrhage from a disrupted medium or small posterior mediastinal vessel, despite the failure to identify the specific vessel at necropsy.

Case 8. Liver failure and hemorrhage. A 57 year old white male physician developed albuminuria in 1952 and was found to have macroglossia, hepatomegaly and a right interlobar effusion. Hemoglobin was 16 gm.%; the urine was acid and concentrated to 1.015, and contained 10 gm. of albumin in a 24 hour specimen. The serum albumin was 2.6 gm.%. Alkaline phosphatase was 9.9 Bodansky units. Bromsulphalein was 20% retained after 45 minutes. Serum cholesterol was 558 mg.%. Liver and tongue biopsies both revealed amyloid disease. By February, 1954, the liver edge was at the level of the iliac crest, and marked peripheral edema had developed. The urine had become and remained persistently alkaline. Non-protein nitrogen had risen to 59 mg.%. In April, 1954, pain developed in both lower extremities, and a large ecchymosis appeared over the right thigh after minor trauma. Petechial lesions appeared on the thorax and upper extremities. Urinary 17-hydroxycorticoid excretion was measured before and after intravenous ACTH. There was good adrenal cortical response (3.37 mg. before and 32.58 mg. after ACTH). In May, 1954, jaundice appeared. In June, 1954, the patient developed pain in the right forearm and hand and lost his radial pulse. An ischemic, painful ulcer developed on the left leg, and no pulse could be felt below the femoral. Serum bilirubin gradually rose to 20.4 mg.%, and alkaline phosphatase to 41.5 Bodansky units. An electrocardiogram was abnormal, showing nondiagnostic ST-T wave changes. In July, 1954, gastrointestinal bleeding developed, the nonprotein nitrogen rose, the patient became acidotic, showed potassium retention, remained deeply jaundiced, became oliguric and comatose, and then died.

At autopsy there were purpuric lesions over the thorax and ischemic necrosis of the lower two thirds of the right leg and foot. There were ascites and hydrothorax. The heart was enlarged, dilated and heavy, and contained amyloid. The liver parenchyma was 90% replaced by amyloid. The spleen, kidneys and both adrenals were also extensively involved. The esophagus and small bowel contained amyloid, and there was blood in the gastrointestinal tract. There was minimal involvement of the bone marrow, prostate and alveolar septa. There was extensive vascular involvement, particularly of the smaller arterioles. Both the aorta and the pulmonary artery showed some involvement of the media. The smaller vessels of the heart, pancreas and gastrointestinal tract contained amyloid. The skin and skeletal muscles did not contain amyloid.

Comment: This case represents primary amyloidosis by virtue of the widespread involvement (including the heart and the tongue), and the absence of pathologic evidence for predisposing disease. Included among the involved organs were the liver, spleen, adrenal and kidney. There was evidence of renal and hepatic failure. This is unusual in the primary group, and again emphasizes the difficulty of classification.

Case 9. Heart failure. In late 1946 a 51 year old white male developed hepatomegaly and ascites. There was 35% bromsulphalein retention after 30 minutes. His heart was enlarged, and the electrocardiogram showed evidence of an old anterior myocardial infarction. Liver biopsy showed amyloid infiltration. By January, 1947, he had marked venous distention, a right pleural effusion, ascites, and edema to the iliac crests. The heart was enlarged to the anterior axillary line. The urine concentrated to 1.021 and contained 1 plus albumin. Nonprotein nitrogen was 34 mg.%. He did not respond to measures for congestive failure, gradually deteriorated, and died on March 21, 1947. Postmortem examination was not permitted.

Comment: Inasmuch as this case clinically represents cardiac and hepatic involvement without known predisposing disease, it must be classified as primary amyloidosis. It is conceivable that the myocardial infarct shown by the electrocardiogram could have been produced by amyloid involvement of the coronary arteries.

Amyloidosis in patients dying of underlying disease:

Case 10. In 1944 an 18 year old white male developed Hodgkin's disease. During the ensuing years he was treated repeatedly with nitrogen mustard, x-ray and TEM. In February, 1952 (eight years after onset), a left lower lobe consolidation and empyema developed. At thoracotomy, in July, 1952, a large empyema cavity was found. The diaphragm was partly destroyed, and the process had extended to involve the spleen. The left lower lobe of the lung, spleen, necrotic diaphragm, a portion of adherent stomach, tail of the pancreas, and tumor-infiltrated left lobe of the liver were removed. None of these tissues contained amyloid. In August, 1952, evidence of impaired renal function appeared. The urine did not concentrate beyond 1.012, contained albumin, and became and remained alkaline. The alkaline phosphatase was 30.5 Bodansky units. In December, 1952, the possibility of amyloid disease was considered, but Congo red was only 46% retained by the tissues. Over the next three months the temperature remained elevated, the left chest continued to drain purulent material, and the white count remained above 40,000. The patient's weight fell to 88 pounds, and he died in March, 1953, essentially of persistent sepsis and profound inanition.

Postmortem examination revealed extreme emaciation, a large left empyema cavity, and Hodgkin's involvement of lungs, liver, left adrenal, diaphragm and retroperitoneal lymph nodes. There was moderate amyloid infiltration of the kidneys and liver, right adrenal, stomach, pancreas and small arterioles.

Case 11. In 1942 a 50 year old white male developed a persistent cough. There was no evidence of pulmonary infection or malignancy. In 1943 left chest pain and hemoptysis occurred, and a diagnosis of carcinoma was made on the basis of a bronchoscopic biopsy of the left main stem bronchus. The lesion was deemed inoperable, and between 1943 and 1946 the patient received three courses of x-ray therapy. In April, 1947, the liver was found to be greatly enlarged. The urine concentrated to 1.025, contained 4 plus albumin and was alkaline. Nonprotein nitrogen was elevated. Bromsulphalein was 14% retained after one hour. Congo red was 67% retained by the tissues. Liver biopsy done through a peritoneoscope revealed minimal amyloid involvement. A second biopsy of the left main stem bronchus confirmed the original diagnosis. Increased pulmonary involvement with cavitation gradually developed. The cholesterol rose to 648 mg.%, and hypoalbuminemia became marked (0.7 gm.%). In January, 1948, the patient had a large hemoptysis and the sputum became positive for tuberculosis. Hemoptyses continued and in October, 1948, he died suddenly as a result of a massive pulmonary hemorrhage. Autopsy was not permitted.

Case 12. A 36 year old white male was hospitalized in January, 1948, because of cough and weight loss. He was febrile and had generalized lymphadenopathy and a slightly enlarged liver. There were multiple old fracture deformities of the extremities. One sputum was negative for acid-fast bacilli. Lymph node biopsy revealed no abnormality. X-rays and bone biopsy were consistent with the diagnosis of dyschondroplasia. A chest x-ray showed a pneumonia that slowly cleared with penicillin. An anemia of 8.0 gm. was unexplained. Four years later (1952) he developed massive hepatosplenomegaly. There was no adenopathy. Hemoglobin and albuminuria were present. Nonprotein nitrogen was 51 mg.%; 8.5% of bromsulphalein was retained after 45 minutes. Congo red dye was entirely retained by the tissues. The patient deteriorated rapidly. The nonprotein nitrogen rose to 171 mg.%, creatinine to 11.8 mg.%. The CO_2 combining power fell to 10 m. mol/L. During his last week of life he received 1 gm. of streptomycin daily. He died on March 17, 1952, following a convulsion.

Necropsy revealed miliary tuberculosis. There was a tuberculous pyelonephritis. There was moderate involvement of the liver, kidneys, adrenals and spleen with amyloid, but insufficient involvement of any organ to have caused death.

Comment: These last three patients died of their underlying disease and not of amyloidosis. In case 10, some idea of the time required to develop moderate amyloidosis can be adduced from the interval of time between examination of an uninvolved large multi-organ operative specimen and the postmortem examination (nine months). Hodgkin's disease existed for eight years without amyloidosis, but within a year of the establishment of an empyema, amyloidosis appeared. It seems probable, therefore, that the amyloid was related to the chronic suppuration and not to either the Hodgkin's disease or the therapy he received (nitrogen mustard and x-ray). In case 11 there was the unusual situation of a six year survival with a bronchogenic carcinoma treated by x-radiation only. By clinical evaluation his amyloid disease was extensive but was not responsible for death. Pulmonary fibrosis, cavitation, tuberculosis and carcinoma were all present terminally. Case 12 died of renal failure, but pathologically renal tuberculosis was the cause and not the moderate amyloid involvement.

DISCUSSION

Twelve cases of amyloidosis have been presented. Three of these cases are considered to be primary amyloidosis. Of these one was not verified pathologically (case 9), and one may be construed to be amyloidosis secondary to multiple sclerosis (case 4), an association not previously reported. Only the remaining one (case 8) filled all the requirements for the diagnosis of primary amyloidosis. Classification therefore proved difficult in two of three cases.

The remaining nine are of the secondary form. Of these nine, three cases occurred in patients with arthritis. In two the arthritis was a progressive, disabling form of rheumatoid arthritis. The third had a similar form of arthritis, associated with Reiter's syndrome. Two patients with Hodgkin's disease developed amyloidosis. Both were patients who had

long survivals (eight and nine years). Amyloidosis occurred in two patients with traumatic paraplegia, both of whom had osteomyelitis and chronic draining sinuses. In the remaining two cases (of the nine with secondary form of the disease), tuberculosis played a rôle in one, and tuberculosis, pulmonary carcinoma and infection in the other.

Of the 12 cases, nine died of causes directly related to amyloid involvement of one or more organ systems. The remaining three died of their underlying disease in the presence of mild or moderate amyloid involvement. In these three, death was related to Hodgkin's disease and sepsis (case 10), miliary tuberculosis (case 11), and hemoptysis from combined pulmonary tuberculosis and carcinoma (case 12).

In all 12 cases amyloid disease was suspected ante mortem. In eight cases there was significant Congo red retention, in two there was a false-negative test, and in two the test was not done (table 1). One of the false-negatives (case 9) occurred in a patient with primary amyloidosis. Another case of primary amyloidosis showed 100% retention of the dye,

TABLE 1
Congo Red Retention

Case	% Dye Retained
1	90
2	85
3	66
4	100
5	80
6	100
7	100
8	— (Biopsy)
9	54 (Biopsy)
10	46
11	67
12	— (Biopsy)

emphasizing the variable affinity for Congo red in this form of the disease. The other false-negative (case 10) was obtained in a patient who must have had little amyloid at the time the test was done. A large multi-organ operative specimen contained no amyloid six months prior to the test. Three months after the test he died of his underlying disease, and at that time there was only minimal amyloid involvement.

Congo red tests were repeated in several of the patients. Usually this was not done within five or six months of the original test. In one patient, however, only 25% of Congo red was retained when the test was repeated three weeks after a previous positive (100% retention). This suggests that amyloid can be saturated with the dye for brief periods. One patient died four days after his last Congo red test. The amyloid tissue was still intensely stained at postmortem examination.

In only four of this series of 12 proved cases was more than 90% of Congo red retained. If this level of retention be required to make a positive diagnosis, there will be many false-negatives. The method of Congo red

testing suggested by Unger and associates involves serial determinations and construction of a disappearance curve. We have had insufficient experience with the method to verify its reliability, but it would seem a reasonable method to obviate the inaccuracies of the older method.

Pathologic material was available in all 12 cases. In two the material was obtained by biopsy. The remaining 10 had complete necropsies. Consistent pathologic findings were observed in all cases where amyloid was the cause of death. Involved viscera were greatly enlarged except in two instances. In one of these, adrenal cortical atrophy had been produced by protracted cortisone therapy, and in the second, adrenal cortical necrosis had resulted from adrenal vein thrombosis. The livers were two to three times normal size, the largest weighing 5,900 gm. (table 3). The kidneys were large, contained many totally amyloid effaced renal glomeruli, and showed hydropic degeneration of the tubular epithelium. The adrenal involvement was always maximal in the juxtamedullary region. The adrenal medulla was invariably spared. The livers were usually diffusely involved, with compression replacement of normal hepatic parenchyma. Maximal involvement was observed in the viscera (liver, spleen, kidney, adrenal). Diffuse involvement of arterioles of the gastrointestinal tract, pancreas and prostate also occurred. Involvement of gastric mucosa and villi of small bowel was seen. In only one of the autopsied cases was the heart involved.

Since amyloid is deposited in the arterial wall and perivascularly, continued accretion interposes a block to metabolic exchange and compromises the organ cell by pressure. Failure of specific organs and vascular complications produced the clinical pictures observed.

I. Renal failure. Amyloid is deposited in the glomerular capillary. Capillary permeability is altered and albuminuria results. This is the earliest manifestation of renal involvement. The albuminuria frequently becomes massive and leads to albuminemia and edema—the picture of amyloid nephrosis. As the disease progresses, whole glomeruli become non-functional. Glomerular insufficiency results in azotemia. Organic acids, and anions normally excreted, are retained, and acidosis of glomerular origin results. The tubular vascular supply is derived from postglomerular vessels; therefore, the involvement of the glomerular capillary deprives the tubule of adequate blood supply. The interposition of amyloid between capillary and cell further restricts metabolic activity of the tubular cell. The tubular cells show hydropic degeneration. Tubular insufficiency appears, manifested initially by polyuria and the failure to concentrate urine. As tubular insufficiency progresses, the cations Na^+ and K^+ may not be saved, NH_4^+ not produced and the urine not acidified. Thus, in the presence of acidosis of glomerular insufficiency, acidosis of tubular insufficiency is superimposed. The chemistry of these alterations is worth considering briefly, since it explains the pathophysiology of the chemical deviation observed in the serum and urine of five of this group of patients.

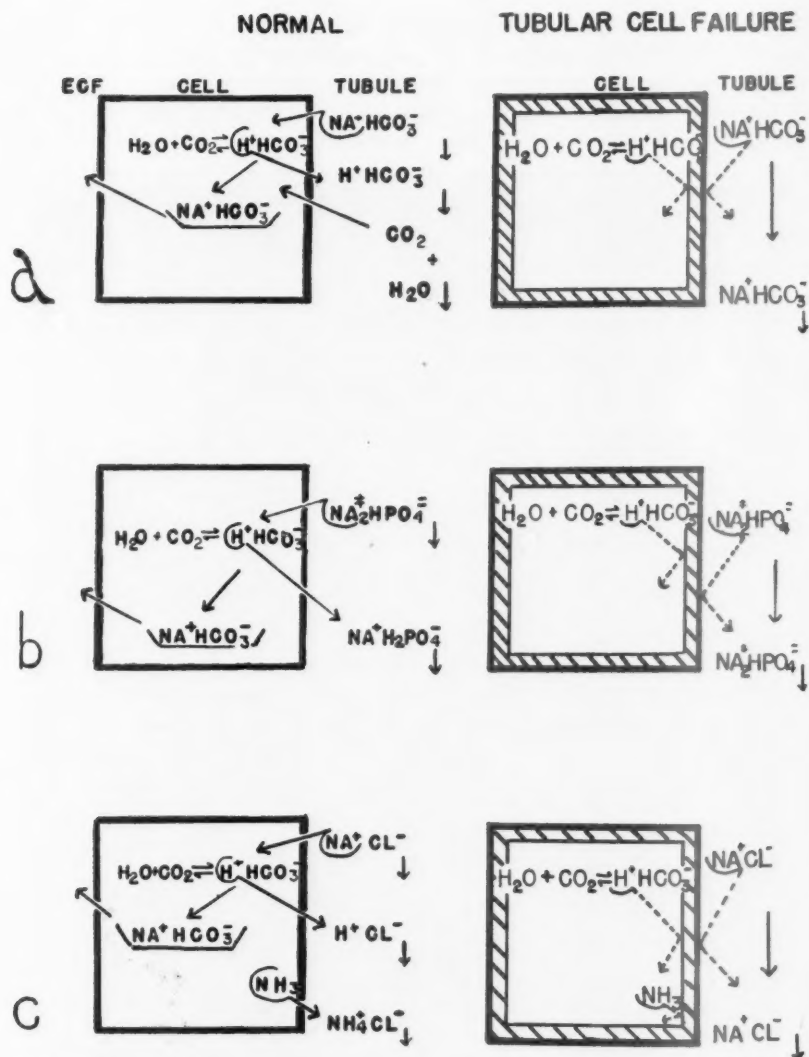


FIG. 1. This is a schematic representation of function of the renal tubular cell in conservation of electrolytes. The diseased tubular cell is compared with the normal. For details see text.

The kidney normally protects and regulates the cation consistency of extracellular fluid by (1) reabsorbing sodium bicarbonate, (2) acidifying the urinary buffer salts, and (3) excreting ammonium ion rather than sodium ion (figure 1).

1. Carbonic anhydrase in the tubular cell catalyzes the reaction $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$, providing H^+ for exchange for Na^+ in the tubule. Na^+ is absorbed, and is returned to the extracellular fluid as bicarbonate. H^+ combines with HCO_3^- in the tubule and becomes H_2O and CO_2 . CO_2 readily diffuses into the cell, where, in combination with H_2O , H^+ HCO_3^-

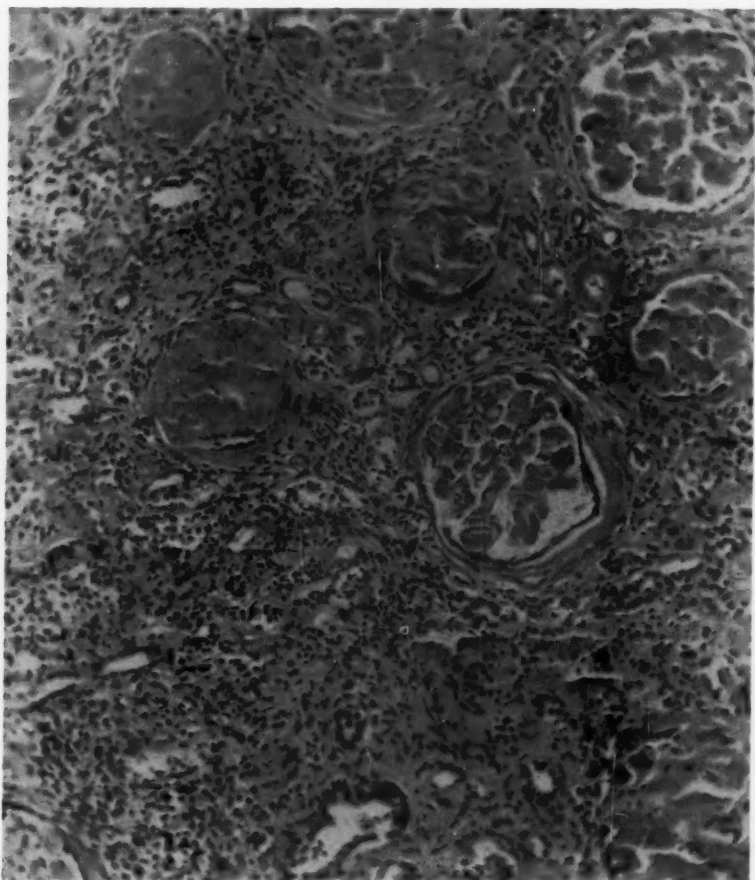


FIG. 2A. Representative section of amyloid involved kidney.

is reformed (the initial step repeated) and another hydrogen ion is made available for excretion (figure 1A).

2. In a similar fashion, H^+ is exchanged for Na^+ , acidifying the buffer salt Na_2HPO_4 (figure 1B).

3. NH_3 is produced in the kidney, diffuses into the tubule, and there is

converted to NH_4^+ , which displace Na^+ as the excretory cation. By this mechanism, not only is a cation saved but a strong acid (HCl) is also removed from the urine. Such an acid would quickly reduce the urinary pH to a point where further H^+ exchange would cease (figure 1C).

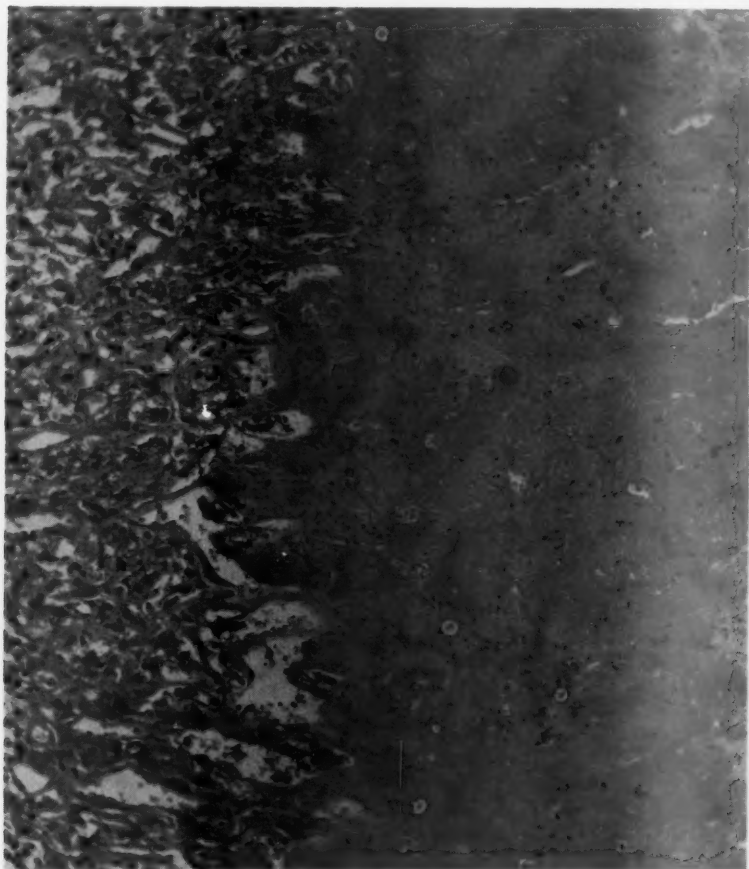


FIG. 2B. Representative section of amyloid involved adrenal.

These mechanisms are dependent upon the integrity of the reaction $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}^+ \text{HCO}_3^-$. In order that this reaction proceed rapidly enough to be functionally significant, carbonic anhydrase is essential. When carbonic anhydrase is inhibited (Diamox administration), or when renal tubular cell failure is present, the following occur: fewer H^+ ions are available, Na^+ is not spared, bicarbonate cannot be saved, NH_4^+ is not produced,

and an obligatory cation (Na^+) diuresis occurs (figure 1). The urine becomes alkaline and an acidosis of renal tubular origin is produced.

All 12 cases showed evidence of renal amyloidosis (table 2). Albuminuria was present in all, and in nine was massive. Eight showed inability to concentrate urine. Six patients showed evidence of renal failure, with

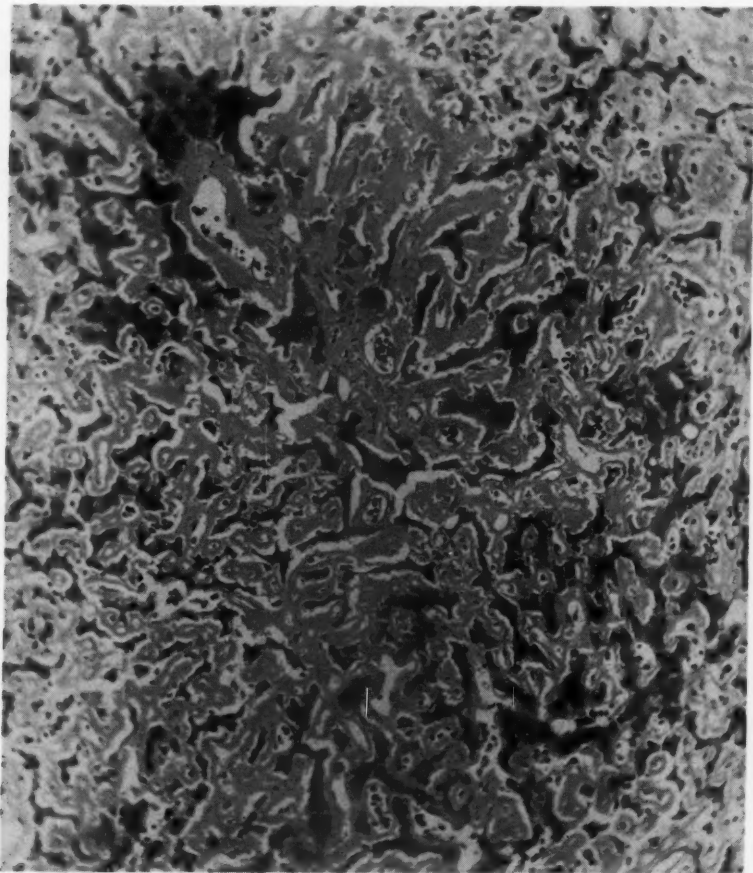


FIG. 2C. Representative section of amyloid involved liver. Note the infiltrative replacement of normal parenchyma, strikingly exemplified in the liver.

fixed specific gravity, albuminuria, elevated nonprotein nitrogen and lowered serum bicarbonate. In five of these (cases 1 to 5) there was no renal disease save amyloidosis. The sixth (case 12) had renal failure secondary to tuberculous pyelonephritis. In all cases serological test for syphilis was negative.

In the five cases of renal failure due to amyloidosis (table 2, cases 1-5), alkaline urines were present in the face of severe acidosis (CO_2 4.7 to 13.5 m. mol/L.). Serum chloride in these cases was either normal or slightly increased. Sodium and potassium levels were normal, except in two individuals who developed adrenal cortical insufficiency. The discrepancy

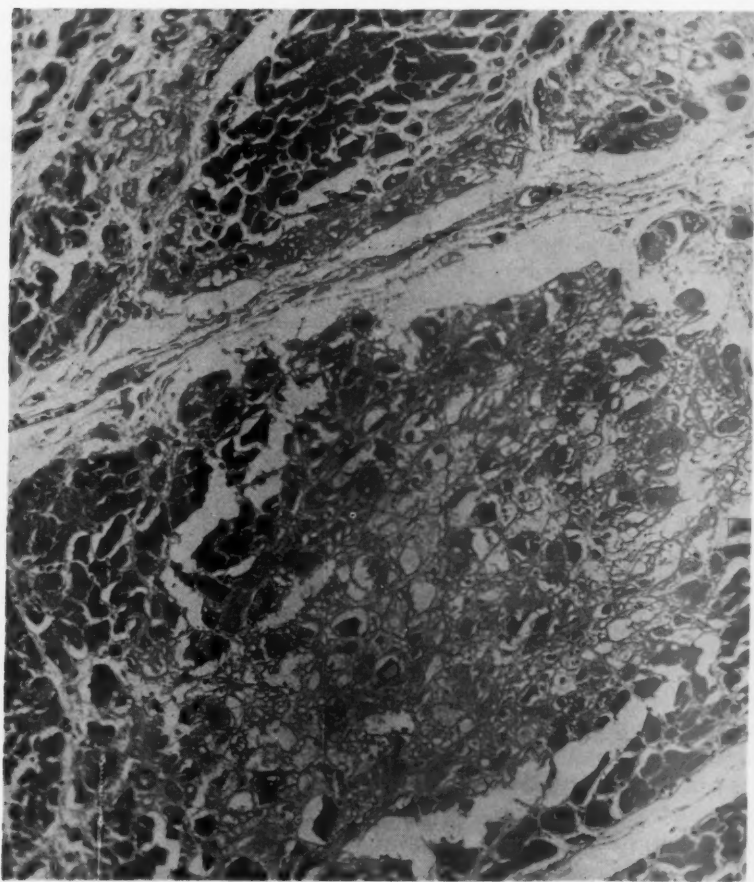


FIG. 2D. Representative section of amyloid involved heart.

between measured cation and anion is explained by increased level of inorganic phosphorus (9 to 12 mg.%), retention of organic acid radicals, and slightly elevated chloride. The significance of these findings was not originally appreciated, and in one patient only (case 1) were urinary electrolytes measured. On two determinations 134 and 120 mEq. of Na^+ and

194 and 175 mEq. of K^+ were excreted in 24 hour periods. As a result of these findings, a recently observed living case with similar urinary findings, elevated nonprotein nitrogen and 100% Congo red retention was more extensively studied. Repeated determinations showed daily urinary excretion of 200 to 300 mEq. of Na^+ and 50 to 70 mEq. of K^+ . We feel that these observations substantiate the occurrence of renal tubular acidosis, and suggest that such is a fairly frequent manifestation of amyloid-induced renal failure.

II. *Adrenal cortical failure.* Adrenal cortical hypofunction has been reported rarely in amyloidosis.^{8, 33} Stemmerman reported no incidence in a series of 468 cases of amyloidosis,⁴⁸ yet O'Donnell³⁶ lists amyloid as the third most common cause of Addison's disease. Many reports of amyloidosis are in pathology series, which do not indicate whether amyloid was the cause of death or merely an associated finding. If the cause of death

TABLE 2
Manifestations of Renal Disease

Case	S. G.	Albumin Gm./24 Hrs.	Reaction	NPN	CO ₂
1	1.012	9.7 gm.	Alkaline	80-100	5
2	1.010	(4+)	Alkaline	55-75	4.7
3	1.010	7.5	Alkaline	70-80	8.5
4	1.011	8.0	Alkaline	61	13.5
5	1.010	(4+)	Alkaline	60-80	10.
6	1.020	10.	Acid	30	Normal
7	1.018	(2+)	Acid	30	Normal
8	1.010	10.	Alkaline	30	Normal
9	1.020	(1+)	Acid	30	Normal
10	1.012	(2+)	Alkaline	20	Normal
11	1.025	(4+)	Alkaline	30	Normal
12	1.011	(4+)	Acid	171	10

is the underlying disease, it is understandable that the associated amyloidosis may not have progressed sufficiently to cause organ failure. The adrenals in this series, like other amyloid-involved organs, were enlarged in all cases except in the instances (case 3) where necrosis had resulted from adrenal vein thrombosis, and (case 6) where cortisone-induced atrophy had occurred. None of the cases escaped involvement of the adrenals, but only two showed good clinical evidence of adrenal cortical insufficiency. In none of the cases was the adrenal medulla involved. The cortex was variably involved—always, however, with the juxtamedullary layers most heavily infiltrated. We have no explanation of why this distribution should exist. It is interesting to speculate that the secretory products of an organ might determine its affinity to amyloid.

To produce hypofunction of the adrenal cortex, almost complete replacement is required. This is demonstrated in case 8, who had an excellent

response to an ACTH test despite advanced amyloid involvement. There can be little doubt that cases 1 and 3 had adrenal cortical insufficiency. Both responded clinically to cortisone therapy, and both experienced Addisonian crises in association with cortisone withdrawal. Adrenal cortical failure is also offered as an explanation for the terminal events in cases 4 and 5. In case 6 death was due to acute adrenal cortical insufficiency, which was related not to amyloidosis but rather to an unrecognized septicemia in the presence of cortisone suppression of the adrenal cortex. The incidence of adrenal cortical insufficiency is probably higher than the literature indicates. The availability of more accurate methods of measuring adrenal cortical function may make possible earlier recognition of adrenal cortical involvement in amyloidosis.

III. *Liver failure.* Liver involvement is almost universal in secondary amyloidosis, and it occurs in 30 to 40% of cases of primary amyloidosis.

TABLE 3
Manifestations of Hepatic Involvement

Case	BSP (% retention) after 45 min.	Cholesterol (Mg.%)	Alk. P'tase (Bodansky U.)	Serum Bilirubin (direct/ indirect)	Alb./glob. gm. %	C. Flocc. (Degree)	Thymol Turbidity (Units)	P. Time (%)	Liver Wt. (gm.)	Est. Amyloid Involvement (%)
1	4.9	179	14.2	0.2/0.4	2.4/3.3	0	2.0	63	4,000	90
2	10.0	—	3.9	0.2/0.2	1.8/3.6	0	1.0	—	2,850	80
3	—	—	—	—	—	—	—	—	—	—
4	32.0	604	45.0	0.2/0.2	1.3/4.7	0	0.6	100	3,350	75
5	8.8	—	1.6	0.2/0.2	4.2/2.1	—	—	—	2,150	50
6	40.0	740	25.0	0.2/0.4	0.8/5.4	4+	10.0	43	5,900	90
7	54.0	—	7.0	0.2/0.4	4.9/3.2	0	1.0	100	4,000	75
8	22.0	600	41.0	20.4 (total)	2.6/2.5	0	—	100	3,800	90
9	35.0	225	—	—	3.3/1.8	0	—	—	—	—
10	—	—	30.0	—	1.5/1.8	0	1.0	—	1,420	50
11	14.0	600	6.1	0.2/0.2	3.3/1.8	0	1.0	—	—	—
12	8.5	153	12.6	0.2/0.2	4.1/3.2	0	1.6	50	3,800	50

Only rare cases of jaundice have been reported;^{34, 45, 60} most reports have dealt with other manifestations of amyloid-induced hepatic dysfunction.⁵¹

Eight of nine livers whose weights were recorded were enlarged; many were massive, with a weight of 5,900 gm. recorded in one instance. Amyloid accounted for 50 to 90% of the recorded weight (table 3). By virtue of the distribution of hepatic amyloid, it could be anticipated that a picture of intrahepatic block would be observed and that, if the process became sufficiently extensive, parenchymal failure could be produced. It was surprising in the present series to observe the extreme degrees of bromsulphalein retention, elevation of alkaline phosphatase, and cholesterol in association with normal serum bilirubins (table 3). The degree of impairment of excretory function was almost invariably associated with lack of evidence for other hepatic dysfunction.

Bromsulphalein retention was greater than 5% after 45 minutes in nine

of the 10 cases so studied. In four the retention was minimal (8.5%, 8.8%, 10% and 14%), but in the remaining seven it was elevated from 22% to 54%. Alkaline phosphatase was elevated in eight of the 10 cases. Extremely high elevations were noted in four cases (45, 25, 41 and 30 Bodansky units). The cholesterol level was greater than 500 mg.% in four of seven cases. Serum bilirubin was normal except in one patient (case 8). In this instance jaundice was present preterminally (bilirubin, 20 mg.%). Hypoalbuminemia was present in nine of 11 cases. It seems probable that this can be better correlated with the universally present massive albuminuria than with hepatic dysfunction. The cephalin flocculation and thymol turbidity were significantly altered in only one case.

Except for the preservation of a normal serum bilirubin, the chemistry of the hepatic alteration produced by amyloid mimics that of biliary obstruction. Other intrahepatic disease, such as metastatic carcinoma and hepatoma, may also produce a fragmentary picture of obstruction, with elevation of the alkaline phosphatase as the most characteristic abnormality.

IV. *Heart failure.* Heart failure is a product of replacement of normal muscle by amyloid. Decreased contractility of the organ results in intracardiac congestive failure. Cardiac failure in this disease has been mistaken for constrictive pericarditis. This is not unreasonable, since amyloid, in essence, must produce restrictive involvement of the myocardium. There are no identifying characteristics of amyloid heart disease other than its refractility to therapy. The electrocardiogram usually shows nothing more than nonspecific T wave changes. Suspicion of the true nature of the heart disease must come from evidence of additional organ involvement. Amyloid heart disease was undoubtedly the cause of death in case 9, and may well have been the cause of the electrocardiographic changes suggesting infarction (autopsy not allowed). In case 8 there was amyloid heart disease, but death was due to amyloid involvement of other organs.

V. *Peripheral vascular failure.* When amyloid infiltrates the media of smaller vessels, the elastica is replaced, the vessel is weakened, and hemorrhage and thrombosis may occur. Case 7 terminated of exsanguination purely as a result of amyloid vascular involvement. Three cases had gastrointestinal bleeding that led to death, two had arterial occlusion, which, in one, terminated in ischemic necrosis of an extremity. In none of the cases who bled was there evidence of impairment of the clotting mechanism.

VI. *Gastrointestinal tract involvement.* The gastrointestinal tract was intrinsically involved in cases 1, 6, 7, 8 and 10, but all cases showed some degree of involvement of the submucosal vessels. In the five instances of intrinsic involvement, the usual site of deposition was in the mucosa of the stomach and the villi of the small bowel. Diarrhea occurred in two cases. In three cases of extensive amyloidosis (cases 1, 7 and 8), gastrointestinal hemorrhage resulted in death. Steatorrhea and malabsorption (impaired oral glucose tolerance test) have been reported in amyloidosis.⁵²

VII. *Blood picture.* Most patients showed anemia related to their underlying disease. However, in two instances (both cases of primary amyloidosis) a high hemoglobin and hematocrit were observed. Amyloid involvement of the bone marrow was demonstrated in one of these cases. The possibility is suggested that amyloid involvement of the bone marrow can produce anoxia and lead to polycythemia. Polycythemia in primary amyloidosis with marrow involvement has been previously reported.⁵⁹

VIII. *Blood pressure.* Despite the frequency of significant renal disease, hypertension was not observed. Only two patients displayed moderate elevation of the blood pressure. Both of these patients had been on ACTH or cortisone in excess of 20 months and showed obesity, striae, moon face, osteoporosis and, in one case, glycosuria. Neither showed renal failure; both concentrated urine well and had normal nonprotein nitrogens. Their blood pressure elevation was believed to be related to their ACTH and cortisone therapy. Elevated blood pressure was so conspicuously absent otherwise that we believe its presence in renal amyloidosis is fortuitous.

IX. *Miscellaneous.* Patients with amyloid disease may be unusually susceptible to infection. Septicemia was recorded in four patients (two pneumococcus, one beta hemolytic streptococcus, one *Aerobacter aerogenes*). An additional patient had metastatic abscesses at post mortem.

One patient who had biopsy-verified Hodgkin's disease, and who had repeated satisfactory responses to nitrogen mustard, TEM, and x-ray, died after nine years with extensive secondary amyloidosis. At necropsy there was no evidence of Hodgkin's disease. The paucity or absence of Hodgkin's disease under these circumstances has been previously observed.⁵ Since it is possible to produce amyloidosis with nitrogen mustard experimentally, these observations suggest that it may be the therapy, and not the Hodgkin's disease, that is responsible for the amyloidosis.

TREATMENT

There is no known satisfactory therapy for either primary or secondary amyloidosis. Crude liver extract and ACTH and cortisone have been recommended.^{19, 14} Some of this series of patients were treated with crude liver preparations, without discernible benefit. Others either developed amyloidosis while on ACTH or cortisone, or received such therapy without improvement. Treatment for the large part was directed at the underlying disease or at the manifestations of amyloidosis. In a few instances, recognition of a treatable complication (i.e., adrenal cortical insufficiency) prolonged life, but in all instances the amyloid disease progressed to termination without measurable remission.

SUMMARY

The nature, incidence, pathology, pathogenesis and clinical manifestations of amyloidosis are discussed.

Twelve cases of amyloidosis are presented. Of these, three are considered to be of the primary and nine of the secondary variety. These three cases of primary amyloid disease bring to about 100 the cases reported in the literature to date. The nine cases of secondary amyloidosis are related to arthritis in three instances, to Hodgkin's disease in two, to infections occurring in traumatic paraplegia in two, and to tuberculosis and carcinoma in one each. Nine of the cases died of amyloidosis. Three died of their underlying disease. Pathologic verification of the disease was made in all 12; in 10 complete necropsy was done. The Congo red test established the diagnosis in eight of 10 cases.

All had evidence of renal disease, and five cases had renal tubular acidosis and died of renal insufficiency.

Two cases of adrenal cortical insufficiency due to amyloid disease are reported.

Hepatic function was altered in all, and jaundice was present in one instance. The chemistry of the hepatic disturbance closely resembled that of obstructive hepatic disease.

Involvement of the vascular tree led to thrombotic episodes in two cases and to massive hemorrhage in three. Gastrointestinal hemorrhage and diarrhea were observed as evidence of intestinal amyloidosis.

Comment is made on the frequency of septicemia, the absence of hypertension, and the nature of myocardial involvement in this disease. A suggestive relationship is noted between the appearance of amyloidosis and the use of nitrogen mustard in Hodgkin's disease.

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SUMMARIO IN INTERLINGUA

Amyloidosis es un morbo generalisate que es characterisate per le deposition de un complexo de proteina e polysaccharido in le vasos sanguinee e in le tessutos conjunctive perivascular. In iste sitos, disfallimento de organos specific resulta in parte ab necrosis pressori de cellulas e in parte ab obstruction de normal activitates metabolic. Iste concepto pathophysiologic explica le diversitate del manifestationes de amyloidosis. Le litteratura reporta circa 100 casos de amyloidosis sin morbo antecedente (i.e. amyloidosis primari). Circa 50 pro cento de iste casos se terminava in disfallimento cardiac. Amyloidosis secundari occurre como un complication commun de tuberculose, arthritis rheumatoide, e myeloma multiple. In series autoptic, inter 15 e 25 pro cento del casos del mentionate tres morbos se revela como complicate per amyloidosis. Le condition ha etiam essite reportate in casos de osteomyelitis, sepsis chronic, morbo de Hodgkin, carcinoma, leucemia, e subacute endocarditis bacterial.

Es presentate un reporto de dece-duo casos de amyloidosis. In tres illo pareva esser primari, in nove secundari. Materiales pathologic esseva disponibile in omne 12 casos. Necropsias complete esseva reportate pro 10. Le forma secundari del morbo esseva associate con arthritis in tres casos, con morbo de Hodgkin in duo, con paraplegia traumatic con osteomyelitis in duo, con carcinoma in un, e con tuberculose

etiam in un. In octo ex 10 casos, rubio congo esseva retenite in ultra de 60 pro cento. Duo reactiones esseva false negative. In un de iste casos le amyloidosis esseva minimal, in le altere il se tractava del forma primari del morbo. Omne le 12 casos manifestava affectiones renal. In sex casos, le patientes moriva con disfallimento renal. In cinque casos le disfallimento renal esseva characterisate per nephrosis amyloide, elevate valores de nitrogeno non-proteinic, e urina alcalin in le presentia de extreme acidosis metabolic. Iste ultime constatacion es explicate per le incapacitate de conservar natrium e kalium, le perdita de bicarbonato, e le incapacitate de excerner iones de hydronium e ammonium (acidosis reno-tubular). Disfallimento adreno-cortical esseva constatate in duo patientes. Ambes experienciava crises addisonian, e ambes respondeva a cortisona. Un patiente moriva de acute insufficiencia adrenal in le presentia de septicemia. Dysfunction hepatic esseva manifeste in signos de obstruction intrahepatic con marcate elevationes del valores de phosphatase alcalin seral e de cholesterol e un basse excretion de bromsulphaleina. Un sol caso revelava un augmento del bilirubina seral. Tres patientes moriva ab hemorrhagia massive connectite con affection vascular. Thromboses de vasos major occurreva in duo casos. Septicemia esseva demonstrate in cinque casos. Le possibilitate que il existe un relation etiologic inter amyloidosis e le therapia a mustarda a nitrogeno in morbo de Hodgkin es signalate a causa del occurrentia tardive de iste complication e proque amyloidosis pote esser producite experimentalmente per medio de mustarda a nitrogeno. Hypertension non occurreva in le presente serie in despecto de aviantiate morbo renal. Polycythemia esseva presente in duo casos. In un de istos, affection del medulla ossee esseva demonstrabile. Nulle therapia effectuava un remission de forma mesurable. Cortisona, ACTH, e preparatos de hepate crude esseva omnes sin beneficio.

BIBLIOGRAPHY

1. Ballinger, J.: Amyloid heart disease, *Am. J. M. Sc.* **217**: 308-313, 1949.
2. Bannick, E. G., Berkman, J. M., and Beaver, D. C.: Diffuse amyloidosis; three unusual cases; a clinical and pathological study, *Arch. Int. Med.* **51**: 978-990, 1933.
3. Bayrd, E. D., and Bennett, W. A.: Amyloidosis complicating myeloma, *M. Clin. North America* **34**: 1151-1164, 1950.
4. Berris, B., and Wolff, H. J.: Primary systemic amyloidosis with jaundice and hemorrhage, *Gastroenterology* **13**: 67-72, 1949.
5. Case Records of Massachusetts General Hospital, *New England J. Med.* **241**: 497-500, 1948; **252**: 994-999, 1955.
6. Clinico-pathologic conference: Amyloidosis of the liver and cardiac failure, *Am. J. Med.* **17**: 280-290, 1954.
7. Dahlin, D. C.: Amyloidosis, *Proc. Staff Meet., Mayo Clin.* **24**: 637-648, 1949.
8. Dahlin, D. C.: Secondary amyloidosis, *Ann. Int. Med.* **31**: 105-119, 1949.
9. Dahlin, D. C.: Primary amyloidosis with report of 6 cases, *Am. J. Path.* **25**: 105-123, 1949.
10. Dahlin, D. C.: Classification and general aspects of amyloidosis, *M. Clin. North America* **34**: 1107-1111, 1950.
11. Dahlin, D. C., Stauffer, M. H., and Mann, F. D.: Laboratory and biopsy diagnosis of amyloidosis, *M. Clin. North America* **34**: 1171-1176, 1950.
12. Drapiewski, J. F., Sternlieb, S. B., and Jones, R.: Primary amyloidosis with spontaneous rupture of the spleen and sudden death, *Ann. Int. Med.* **43**: 406-412, 1955.
13. Ensign, W. G.: Macroglossia as a manifestation of primary systemic amyloidosis, *J. A. M. A.* **149**: 136-138, 1952.
14. Fiese, M. J.: Primary systemic amyloidosis; therapeutic failure of desiccated liver; report of a case, *Stanford M. Bull.* **11**: 30-32, 1953.

15. Findley, J. W., Jr., and Adams, W.: Primary systemic amyloidosis simulating constrictive pericarditis with steatorrhea and hyperesthesia, *Arch. Int. Med.* **81**: 342-351, 1948.
16. Forbus, W. D.: Reaction to injury—pathology for students of disease, Vol. II, 1952, The Williams and Wilkins Co., Baltimore, pp. 370-378.
17. Gedda, P. O.: On amyloidosis and other causes of death in rheumatoid arthritis, *Acta med. Scandinav.* **150**: 443-452, 1955.
18. Golden, A.: Primary systemic amyloidosis of alimentary tract, *Arch. Int. Med.* **75**: 413-416, 1945.
19. Grayzel, H. G., and Jacobi, M.: Secondary amyloidosis; results of therapy with desiccated whole liver powder, *Ann. Int. Med.* **12**: 39-58, 1938-39.
20. Guttman, P.: Addison's disease, *Arch. Path.* **10**: 742-785, 895-914, 1930.
21. Hass, G., and Schulz, R. Z.: Studies of amyloid. II. The isolation of a polysaccharide from amyloid-bearing tissue, *Arch. Path.* **30**: 240-259, 1940.
22. Higgins, W. H., and Higgins, W. H., Jr.: Primary amyloidosis; a clinical and pathological study, *Am. J. M. Sc.* **220**: 610-615, 1950.
23. Hochman, A., and Czerniak, P.: Hodgkin's disease and amyloidopathia, *Radiology* **63**: 716-721, 1954.
24. Jackson, A.: Amyloidosis: report of 3 cases with some consideration as to etiology and pathogenesis, *Arch. Int. Med.* **93**: 494-502, 1954.
25. Jackson, A., and Slavin, M.: Primary amyloidosis. A report of two cases, *Am. Heart J.* **47**: 839-844, 1954.
26. Jacobi, M., and Grayzel, H.: Generalized secondary amyloidosis; a clinicopathological study of 84 cases, *J. Mt. Sinai Hosp.* **12**: 339-363, 1945.
27. Josselson, A. J., Pruitt, R. D., and Edwards, J. E.: Amyloid disease of heart, *M. Clin. North America* **34**: 1137-1144, 1950.
28. Josselson, A. J., Pruitt, R. D., and Edwards, J. E.: Amyloid localized to the heart—analysis of 29 cases, *Arch. Path.* **54**: 359-367, 1952.
29. King, F. H., and Oppenheimer, G. D.: Rupture of amyloid spleen, *Ann. Int. Med.* **29**: 374-378, 1948.
30. Lindsay, S.: Primary systemic amyloidosis with nephrosis, *Am. J. Med.* **4**: 765-772, 1948.
31. Marriott, H. J. L.: Primary systemic amyloidosis, *Ann. Int. Med.* **38**: 620-626, 1953.
32. Mathews, W. H.: Primary systemic amyloidosis, *Am. J. M. Sc.* **228**: 317-333, 1954.
33. Mendel, D. L., and Saibil, M.: Amyloidosis of adrenals as a cause of Addison's disease, *Canad. M. A. J.* **39**: 457-459, 1938.
34. Moschowitz, E.: The clinical aspects of amyloidosis, *Ann. Int. Med.* **10**: 73-88, 1936.
35. Newmann, W., and Jacobson, A. S.: Paraplegia and secondary amyloidosis—report of 6 cases, *Am. J. Med.* **15**: 216-222, 1953.
36. O'Donnell, W. M.: Changing pathogenesis of Addison's disease with special reference to amyloidosis, *Arch. Int. Med.* **86**: 266-279, 1950.
37. Parker, R. L., Odell, H. M., Logan, A. H., Jr., Kelsey, J. R., Jr., and Edwards, J. E.: Primary systemic amyloidosis; report of 2 cases, *M. Clin. North America* **34**: 1119-1135, 1950.
38. Pocock, D. S., and Dickens, J.: Paramyloidosis with diabetes mellitus and gastrointestinal hemorrhage, *New England J. Med.* **248**: 359-363, 1953.
39. Pirani, C. L., Bly, C. G., Sutherland, K., and Chereso, F.: Experimental amyloidosis in guinea pigs, *Science* **110**: 145-146, 1949.
40. Reece, J. M., and Reynolds, T. B.: Amyloidosis complicating rheumatoid arthritis, *Am. J. M. Sc.* **228**: 554-559, 1954.
41. Reimann, H. A., Sahyoun, P. F., and Chaglassian, H. T.: Primary amyloidosis; relationship to secondary amyloidosis and report of a case, *Arch. Int. Med.* **93**: 673-686, 1954.

42. Richter, G. W.: The reabsorption of amyloid under experimental conditions, *Am. J. Path.* **30**: 239-261, 1954.
43. Selikoff, I. J.: Diagnosis of generalized amyloidosis by Congo red test: definite diagnostic criteria, *Am. J. M. Sc.* **213**: 719-727, 1947.
44. Selikoff, I. J., and Robitzek, E. H.: Gingival biopsy for diagnosis of generalized amyloidosis, *Am. J. Path.* **23**: 1099-1111, 1947.
45. Spain, D. M., and Riley, R. L.: Jaundice in amyloidosis of liver, *Am. J. Clin. Path.* **14**: 284-288, 1944.
46. Stark, D. B., and New, G. B.: Amyloid tumors of larynx and trachea, *M. Clin. North America* **34**: 1145-1150, 1950.
47. Stauffer, M. H.: Hepatic manifestations in secondary amyloidosis, *M. Clin. North America* **34**: 1165-1169, 1950.
48. Stemmerman, M. G., and Auerbach, O.: Adrenal amyloidosis, *Arch. Int. Med.* **74**: 384-389, 1944.
49. Teilum, G., and Lindahl, A.: Frequency and significance of amyloid changes in rheumatoid arthritis, *Acta med. Scandinav.* **149**: 449-455, 1954.
50. Teilum, G.: Studies on pathogenesis of amyloid. II. Effect of nitrogen mustard in inducing amyloidosis, *J. Lab. and Clin. Med.* **43**: 367-374, 1954.
51. Teilum, G.: Cortisone, ascorbic acid interaction and pathogenesis of amyloidosis: mechanism of action of cortisone on mesenchymal tissues, *Ann. Rheumat. Dis.* **11**: 119-135, 1952.
52. Tiber, A. M., Pearlman, A. W., and Cohen, S. E.: Hepatic function in patients with amyloidosis, *Arch. Int. Med.* **68**: 309-324, 1941.
53. Unger, P. N., Zuckerbrod, M., Beck, G. J., and Steele, J. M.: Amyloidosis in rheumatoid arthritis; a report of 10 cases, *Am. J. M. Sc.* **216**: 51-56, 1948.
54. Unger, P. N., Zuckerbrod, M., Beck, G. J., and Steele, J. M.: Study of disappearance of Congo red from blood of non-amyloid subjects and patients with systemic amyloidosis, *J. Clin. Investigation* **27**: 111-118, 1948.
55. Volwiler, W., and Jones, C. M.: Diagnostic and therapeutic value of liver biopsies, with particular reference to trocar biopsy, *New England J. Med.* **237**: 651-656, 1947.
56. Wald, M. H.: Clinical studies of secondary amyloidosis in tuberculosis, *Ann. Int. Med.* **43**: 383-394, 1955.
57. Wallace, S. L., Feldman, D. J., Berlin, I., Harris, C., and Glass, I. A.: Amyloidosis in Hodgkin's disease, *Am. J. Med.* **8**: 552-557, 1950.
58. Wollaeger, E. E.: Primary systemic amyloidosis with symptoms and signs of liver disease; diagnosis by liver biopsy—report of a case, *M. Clin. North America* **34**: 1113-1118, 1950.
59. Wolf, R. L., Hitzig, W., and Otani, S.: Amyloidosis unassociated with predisposing disease, *Arch. Int. Med.* **95**: 141-152, 1955.
60. Zetzel, L.: Hepatomegaly with jaundice due to primary amyloidosis, *Gastroenterology* **8**: 783-787, 1947.

CASE REPORTS

IDIOPATHIC HYPOPARATHYROIDISM: REPORT OF AN UNUSUAL CASE*

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INTRODUCTION

HYPOPARATHYROIDISM most commonly occurs following those cases of thyroid surgery where inadvertent damage to, or removal of, the parathyroid glands has taken place.¹ From the study of such cases and their experimental counterparts in animals, most of the known facts of the physiology and therapy of hypoparathyroidism have been worked out. Much less commonly, hypoparathyroidism is idiopathic, developing without preceding surgery and without other apparent cause.

Actually, if the criteria for the diagnosis of idiopathic hypoparathyroidism are adhered to strictly, there are less than 100 recorded cases.^{2,3,4} These fall into two general groups: a childhood-adolescent group, and a group of cases developing in middle life.² This latter group frequently has gone undiagnosed for many years, as exemplified by a recently reported case in which the condition had been present for over 30 years.³ The case to be reported also went unrecognized for many years.

The cardinal metabolic changes that appear as the hypoparathyroid state develops have been succinctly stated by Albright and Reifenstein,¹ as follows: decrease in the phosphorus excretion in the urine; increase in the serum phosphorus level; simultaneous decrease in the serum calcium level; diminished calcium excretion in the urine. If one administers parathyroid extract to a normal or hypoparathyroid patient, the same four metabolic functions are altered in the opposite direction but in the same sequence: hyperphosphaturia, hypophosphatemia, hypercalcemia, hypercalciuria.

If the above metabolic changes are taken into consideration, the specific criteria for the diagnosis of hypoparathyroidism might be enumerated as follows: low serum calcium; high serum inorganic phosphorus level; absence of a terminal or severe renal insufficiency; normal bones, by x-ray, to exclude rickets or osteomalacia; absence of severe chronic diarrhea; presence of tetany or tetanic equivalents (latent tetany); and frequent presence of cataracts and/or trophic nail changes.² From the clinical standpoint, the symptoms of hypoparathyroidism are frequently not only mild but also varied and vague.^{5,6} There may be present only latent tetany, fatigue and muscular weakness, gastrointestinal irritability, attacks of unconsciousness, mental dulling or frank psychosis,^{7,8,9} palpitation, numbness of the extremities, and/or disturbances in the growth of

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the nails.⁴ The diagnosis must therefore be suspected where certain otherwise unexplainable syndromes occur, particularly in thyroidectomized individuals. It must also be remembered that the condition does occur, rarely, on an apparently idiopathic basis.

CASE REPORT

Before the developments in this case which led to the diagnosis of hypoparathyroidism, the patient seemed a most unlikely one ever to prove unusually interesting. He was a 67 year old white male attorney, married for 27 years but childless, who had complained for years of general weakness, nervousness, irritability, chronic fatigue, depression, anxiety and general lack of well-being. At the age of 46, without previous warning, he had a few grand mal seizures. He had another grand mal seizure at the age of 58, with occasional nocturnal seizures, of which he was not aware, during the interval. After his first seizures he was placed on Dilantin Sodium, gr. 1.5 and phenobarbital, gr. 1.5, at bedtime.

It was felt by the neurologist who saw him in consultation at that time that the seizures represented a "migraine-epilepsy syndrome with a latent idiopathic factor, brought to a discharge level at a relatively late age of onset by a superimposed degenerative and/or vascular factor," all adding up to an essentially poor prognosis. He had many episodes of irritability and spasticity of the colon, with occasional loose stools but no real chronic diarrhea.

At the age of 65 he was operated on for bilateral cataracts which had been present for several years. For a few years he had complained frequently of night cramps in the calves of the legs which had been getting progressively worse. He also had occasional attacks of stiffness in the lower back. For several years his blood pressure had varied between 145/95 and 180/95 mm. of Hg. In March, 1951, the patient complained that his "nerves" were very poor. He was unable to handle strain or excitement. He complained of slipping mentally. He appeared duller and as if he were losing his grasp. In June, 1951, he complained of slight spells or spasms, with momentary loss of steadiness, and as if his mind were "going blank." There was no headache or loss of control associated with the episode; he would just feel tense and shaky. An electro-encephalogram showed slight changes compatible with a diffuse encephalopathy. His general complaints, as well as these new spells, were essentially unresponsive to varied therapy.

It was at this point (September 7, 1951) that the patient was seized suddenly with severe squeezing pressure across his chest which persisted for several hours and was associated with palpitation and rapid heart action. The patient was seen shortly thereafter, with a blood pressure of 120/70 mm. of Hg and a pulse rate of 150 per minute and regular. No signs of heart failure were present. The patient complained of feeling slightly dizzy and nauseated but there was no vomiting. After being given morphine sulfate, gr. $\frac{1}{4}$ by hypodermic injection, and a test dose of quinidine sulfate, gr. iii, the patient was hospitalized. Carotid sinus pressure resulted in marked slowing of the heart rate and decreased strength of contracture, almost to the point of cardiac standstill, but with immediate return of the tachycardia on release of the carotid sinus pressure. An electrocardiogram was taken and treatment was initiated with quinidine sulfate, gr. vi orally every two hours. After the fourth dose of quinidine sulfate the pulse was 88 per minute, and the patient was then maintained on quinidine sulfate, gr. iii every four hours.

The electrocardiogram, confirming the tachycardia as of supraventricular origin, disclosed a prolongation of the QT interval which became even more obvious on the following day (September 8, 1951), when the tachycardia was no longer present (figure 1). Blood chemical determinations the following day revealed a high normal blood urea nitrogen, a low serum calcium, a high serum phosphorus, normal alkaline

and acid phosphatase, and normal serum chlorides, sodium, potassium, carbon dioxide combining power, total protein and blood pH. There was a total absence of calcium from the 24 hour urine specimens (table 1).

Chvostek's sign was moderately positive bilaterally. Following the return of the heart rate to normal the blood pressure gradually rose to 165/90 mm. of Hg, with a pulse rate of 76 per minute on the fifth hospital day.

The findings of low serum calcium, elevated serum phosphorus and absence of calcium from the 24 hour urine specimen were confirmed on three successive days. A bone survey by x-ray revealed a normal roentgenologic appearance of the skull and other bones. The subsequent electrocardiograms also confirmed the prolongation of the QT interval, and never showed more than minor changes suggestive of any definite acute myocardial damage.

On the basis of the above repeated and amply confirmed findings, a diagnosis of probable idiopathic hypoparathyroidism was made and treatment was initiated as follows: Hytakerol (Winthrop-Stearns brand of dihydrotachysterol), two capsules (0.625 mg. each) three times a day before meals; low phosphorus diet, with elimina-

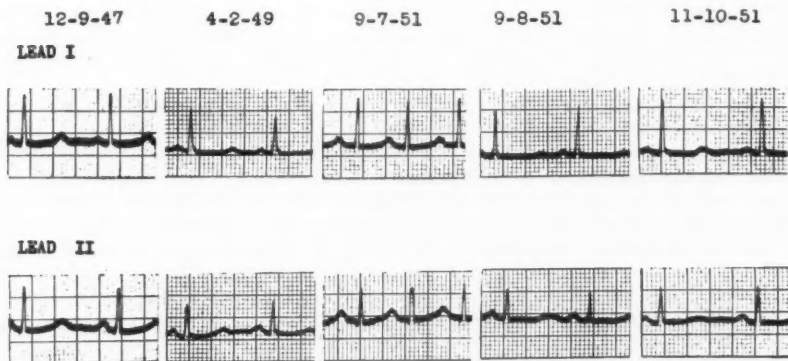


FIG. 1. Leads I and II of electrocardiograms, illustrating QT intervals on dates indicated. Refer to table 1 to see cardiac rate, QT interval and per cent above upper normal of QT interval for respective dates.

tion of milk and milk products; Calglucon (Sandoz), two wafers (1.5 gm. each) three times a day; glutamic acid-HCl, one capsule three times a day before calcium wafers; and Gelusil, one teaspoonful, three times a day immediately after meals.

On this program the serum calcium and phosphorus and the urine calcium returned promptly to normal levels. This response and the return of the QT interval of the electrocardiogram to normal in one week, as indicated in table 1, appeared dramatically conclusive. At this time the patient commented that he felt stronger and was more relaxed and less nervous than he had been for a long time.

The patient was taught to do a Sulkowitch test on his own overnight urine daily, and was kept on a therapeutic program designed to maintain a moderate urinary excretion of calcium. This maintenance program consisted of a diet low in phosphorus, supplemented by calcium wafers and Hytakerol. After a time calciferol was substituted for the Hytakerol because it was much less expensive and was adequately effective for maintenance therapy.

On this program the patient continued to thrive except for one setback, in June, 1953, when, due to overtreatment, he developed hypercalcemia with associated ag-

TABLE 1

Attack of tachycardia, leading to diagnosis of idiopathic hypoparathyroidism, occurred September 7, 1951. Note that the QT interval was actually prolonged, although unrecognized in 1947 and 1949. (For further details, see text.)

Year	1951																			
	1947	1949	Month and day																	
	12/9	4/2	3/15	6/28	9/7	9/8	9/10	9/11	9/12	9/13	9/14	9/15	9/16	9/17	9/18	9/19	9/26	10/2	11/7	11/10
Blood urea nitrogen mg./100 c.c. blood			23	25		22.7		21.8											20	
Blood creatinine mg./100 c.c. blood			1.0			2.0														
Serum calcium mg./100 c.c. serum								7.6	6.6	6.8					8.8	8.2		8.5	9.5	
Serum phosphorus mg./100 c.c. serum								5.9	6.7	6.7					4.9	3.8		5.0	4.3	
Urine calcium (24 hour) mg./100 c.c. urine										0	0	0	0	trace	0.5	37.5	42			
Cardiac rate	75	75	78		132	82	70			72					74		70			68
QT interval (sec.)	.44	.48	.48		.38	.54	.54			.52					.44		.44			.44
QT upper normal (sec.)	.42	.42	.41		.30	.39	.43			.42					.42		.43			.43
% over upper normal	5	14	17		27	33	26			24					5		5			2

TABLE 2
Severe symptoms of hypercalcemia, renal insufficiency and vitamin D toxicity gradually became evident several days before June 5, 1953
(For further details, see text.)

Year	1952										1953										1954				
	3/25	10/24	1/14	1/30	6/5	6/6	6/7	6/10	6/11	6/15	6/18	6/25	7/6	8/20	10/14	12/7	3/27	6/15	7/24	9/16					
Blood urea nitrogen mg./100 c.c. blood		16			69	61		52	54	38	38	34	29.7		19	23	16.5	31	19	15					
Blood creatinine mg./100 c.c. blood					5.0	5.0	5.0		4.3	4.1	3.4	3.1	2.7	2.4		2.2	1.8	1.9							
Serum calcium mg./100 c.c. serum	8.7	8.6		9.6	13.0		13.0	12.1		10.0	9.4	9.0		8.1		8.8	9.8	8.8		8.4					
Serum phosphorus mg./100 c.c. serum	3.5	4.1		3.6			5.7	5.1		3.7	3.7	3.8		4.5		3.9	3.9	4.2		4.9					
Cardiac rate	70	70	83		80									75				66							
QT interval (in seconds)	.44	.44	.36		.38									.44				.45							
QT upper normal (in seconds)	.43	.43	.39		.40									.42				.44							
% over upper normal	2	2	—		—									5				2							

gravation of renal insufficiency, hypertension and severe toxicity. This episode gradually corrected itself when vitamin D therapy and extra calcium were withheld and extra fluids were given. After the serum calcium dropped to 8.1 mg.% it was decided to reinstate the therapeutic program for hypoparathyroidism (table 2).

Aside from the above episode, from which the patient recovered completely, his generally improved state has been essentially maintained now for a period of over four years. He has been much less nervous and definitely more relaxed. He has had no manifestations of his spastic colon, and his Chvostek's sign has remained negative. His whole mood and outlook have changed; in fact, the personality change has been most dramatic. He became again, in his 70's, an active practicing attorney.

COMMENT

All of the criteria outlined above for the diagnosis of idiopathic hypoparathyroidism were met in this patient. His dramatic response to therapy, with complete normalization of his serum calcium and phosphorus, of his urine calcium and of the QT interval of his electrocardiogram, along with his excellent clinical response, added further confirmation to the diagnosis of this relatively rare condition. Probably the most outstanding therapeutic response was in his personality and emotional status. A tense, anxious, fatigued, shaky, supposedly neurotic and deteriorated man became a relaxed, alert attorney, able to carry on his work. A similar case in a 61 year old widow with apparent mental deterioration, confusion and loss of memory, associated with idiopathic hypoparathyroidism, was recently reported.⁷ This patient also showed remarkable improvement with therapy.

The one setback due to overtreatment emphasized the importance of following the urine calcium with a daily Sulkowitch test to prevent this from happening. It might be emphasized here that the toxic reactions of hypervitaminosis D and hypercalcemia, with consequent uremia, are actually much more dangerous in the acute sense than are the symptoms of slight undertreatment of the hypoparathyroidism. This episode also inadvertently gave us the opportunity to show that the patient, without any treatment, would slip back slowly into his previous hypocalcemic state.

It would be mere speculation to attempt to date the time of onset of this patient's hypoparathyroidism and hypocalcemia, or to state that all of his problems were totally dependent upon this. In retrospect, the QT interval of his electrocardiogram was significantly prolonged several years before the diagnosis was made in September, 1951 (figure 1 and table 1). His cataracts could have had a senile causative factor, or could have been entirely from the hypoparathyroidism. The "epilepsy" was undoubtedly a hypocalcemic phenomenon, as was undoubtedly a major portion of his emotional instability, tension and personality change, which proved to be so dramatically reversible with treatment.

One other question that really cannot be answered with certainty is the relationship of the cardiac attack to the hypocalcemia and hypoparathyroidism. One cannot deny that this man in his late 60's had generalized arteriosclerosis, hypertension and probable coronary disease. The attack, however, was definitely associated with a supraventricular tachycardia, and it is interesting to speculate whether this tachycardia might not have been set off, at least in part, by the hypocalcemia. There is some evidence at least that supraventricular tachycardia in dogs may be set off by hypocalcemia.¹⁰

TABLE 3

Year	1955												1956							
	12/21	12/22	12/23	12/23*	12/24	12/25	12/26	12/27	12/29	12/31	1/9	1/19	1/23	1/27	1/30	2/3	2/8	2/13	2/17	2/21
Urea nitrogen, mg. %	25			29	37	43	37.5	42	34		12	21	26	33	25		20	15		
Creatinine, mg. %	2.2			2.8	3.2	2.7	2.4	3.2	2.0		2.1	3.6	3.7	4.8	4.6		3.8	3.6		
Calcium, mg. %	6.5	7.0	6.0	7.2	7.3	6.8	9.6	9.6	8.7	9.1	9.2	10.2	11.4	12.2	11.6	13.0	11.0	10.8	8.5	9.0
Phosphorus, mg. %	2.2	3.6	4.0	QNS	5.4	3.6	6.6	6.3	3.5	2.7	3.9	6.2	5.2	5.0	3.6	3.9	4.0	3.2	3.7	3.5
Alk. phosphatase, U			6.3																	
Chlorides, mEq.				102	106	103	101	98	98		114				95					
Potassium, mEq.				3.6	3.3	3.2	3.2	5.5		4.0	4.0				3.1	3.6		4.1		
Sodium, mEq.				133	132	135	139	142			149				138					
CO ₂ , mEq.				QNS	24.3	17.0	25.6	25.7			23				31					
A/G ratio, gm.				4.1/2.8																
Urine—24 hr. vol., c.c.				950	950	2000	3375	1300	2350	2190	1750									
Urine—calcium, mg. %				14.6	1.9	2.8	5.1	10.7	10.8	12.8	7.6									
24 hr. urine calcium, mg. %				139	17.8	56	172	150	254	279	134									
Transaminase, U	24	25																		
BSP—liver function, (5 mg. per kilo.—45 minute specimen)													2%							
Blood sugar, mg. % (2 hr. p.c.)													145							

* 8 P.M.

SUMMARY AND CONCLUSIONS

1. Idiopathic hypoparathyroidism is a rare condition, as evidenced by the relatively few reported cases.

2. The sequelae of hypoparathyroidism and the clinical criteria for the diagnosis of idiopathic hypoparathyroidism are presented.

3. A case fulfilling all of the criteria for the diagnosis of idiopathic hypoparathyroidism is reported in detail. The hypoparathyroidism in this case was undoubtedly present but undiagnosed for many years. Response to specific therapy was dramatic.

4. Special emphasis is put upon the reversible emotional and psychologic changes in mild chronic hypoparathyroidism.

ADDENDUM

Very recently the patient whose case is reported had another very serious relapse, his hypoparathyroidism becoming sharply out of control despite apparent close observation. Once again he was hospitalized with severe chest pain, vomiting and a picture superficially mimicking a "heart attack." This time, his picture was complicated by a severe urinary infection. He remained critically ill for six days, with a grand mal seizure on one occasion and with definite, almost fatal laryngospasm on several occasions. He was essentially unresponsive to usual therapy with huge doses of dihydrotachysterol and parenteral as well as oral calcium, and did not respond favorably until 3 c.c. of parathyroid hormone were given parenterally. As can be seen from the data of this admission (table 3), several discrepancies occurred this time which confused the picture and are not fully explained, namely, the apparent presence at first of calcium in the urine, and the low phosphorus level (possibly due to complicating renal disease in an old man and/or the prolonged therapy with a low phosphorus diet, producing a depletion of phosphorus stores in the bones). In all subsequent responses, and particularly in the dramatic response to parathyroid hormone when he seemed critical, the patient once again confirmed for us the diagnosis of hypoparathyroidism. He is now again stabilized and well controlled with added calcium and daily calciferol adjusted to his serum calcium level. We have not felt it safe to adjust his dosages any longer by his urine Sulkowitch reaction alone.

SUMMARIO IN INTERLINGUA

Hypoparathyroidismo idiopathic, occurrente sin previe intervention chirurgic e sin altere causa evidente, es un condition rar que es documentate in minus que 100 casos.

In le curso del disveloppamento del stato hypoparathyroide le principal alterationes metabolic a notar es: reduction del excretion urinari de phosphoro; augmento del nivello seral de phosphoro; reduction simultanee del nivello seral de calcium; e reduction del excretion urinari de calcium. Si extracto parathyroide es administrate a un subjecto normal o a un patiente hypoparathyroide, le mesme quatro functiones metabolic es alterate in le direction contrari sed in le mesme ordine: il occurre hyperphosphaturia, hypophosphatemia, hypercalcemia, e hypercalciuria.

Le criterios specific pro le diagnose de hypoparathyroidismo es le sequente: Basse nivellos seral de calcium; alte nivellos seral de phosphoro inorganic; absentia de insufficientia renal terminal o sever; roentgenogrammas ossee normal e ergo capace

a eliminar rachitis o osteomalacia; absentia de sever diarrhea chronic; presentia de tetania o de equivalentes de illo; e presentia in multe casos de cataractas e/o trophic alterationes unguis. Ab le puncto de vista clinic le symptomatas de hypoparathyroidismo es frequentemente leve, variate, e vage. A vices illos consiste solamente de tetania latente, fatiga e debilitate muscular, irritabilitate gastrointestinal, attaccos de perdita de conscientia, reduce acuitate mental o psychosis de forma franc, palpitation, torpor del extremitates, e/o disturbance in le crescentia del unguis.

Es reportate in detalio un caso que satisfice omne le criterios del diagnose de hypoparathyroidismo. In iste caso le hypoparathyroidismo esseva certo presente ben que non diagnosticate durante multe annos. Le responsa al therapia esseva dramatic. Es sublineate specialmente le reversibilitate del alterationes emotional e psychologic que occorre in casos de leve hypoparathyroidismo chronic.

BIBLIOGRAPHY

1. Albright, F., and Reifenstein, E. C.: Parathyroid glands and metabolic bone disease, 1948, Williams and Wilkins Company, Baltimore, pp. 10, 11, 27, etc.
2. Drake, T. G., Albright, F., Bauer, W., and Castleman, B.: Chronic idiopathic hypoparathyroidism: report of six cases with autopsy findings in one, *Ann. Int. Med.* 12: 1751, 1939.
3. Steinberg, H., and Waldron, B. R.: Idiopathic hypoparathyroidism; an analysis of fifty-two cases, including the report of a new case, *Medicine* 31: 133-154, 1952. (This reference includes an extensive bibliography, to which the interested reader is referred.)
4. Sutphin, A., Albright, F., and McCune, D. J.: Five cases (three in siblings) of idiopathic hypoparathyroidism associated with moniliasis, *J. Clin. Endocrinol.* 3: 625, 1943.
5. Levy, H. A.: Unusual clinical manifestations of chronic hypoparathyroidism (treatment with dihydrotachysterol and calcium), *M. Clin. North America* 31: 243, 1947.
6. Haines, S. F.: Parathyroid insufficiency, *M. Clin. North America* 24: 1019-1026, 1940.
7. Robinson, K. C., Kollberg, M. H., and Crowley, M. F.: Idiopathic hypoparathyroidism presenting as dementia, *Brit. M. J.* 2: 1203-1206 (Nov. 20), 1954.
8. Greene, J. A., and Swanson, L. W.: Psychosis in hypoparathyroidism with report of five cases, *Ann. Int. Med.* 14: 1233, 1941.
9. Scarlett, E. P., and Houghtling, W. J.: Psychosis in hypoparathyroidism, *Canad. M. A. J.* 50: 351, 1944.
10. Craddock, C. G.: Personal communication.

ACUTE MASSIVE DIGITOXIN POISONING: REPORT OF A CASE AND REVIEW OF THE LITERATURE *

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THE opportunity to observe myocardial and metabolic responses to massive digitoxin poisoning was recently afforded us by a patient who ingested 75 tablets of digitoxin with suicidal intent. The salient clinical and electrocardiographic manifestations of previously reported cases of poisoning from digitalis and related glycosides are summarized in table 1.¹⁻⁵

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TABLE 1—Clinical Observations of Massive Digitalis Poisoning

Authors	Date Reported	Amount of Drug	Age, Sex	Heart Disease	Rhythm	Clinical Effects	Electrocardiographic Manifestations	Comments	Outcome
Tomazewski and Lapa ¹	1936	10 c.c. Digitaline Nativelle	23F	None	Normal sinus with premature contractions	Nausea, vomiting, abdominal pains, diarrhea, vertigo, headache, syncope lasted 7 days. Albuminuria and cylindruria	Low voltage 2:1 atrioventricular block. Later, normal sinus rhythm with ventricular premature contractions. ST changes. Variable atrioventricular block, never complete	Normal EKG after 14 days	Recovered
McGuire and Richards ²	1936	6-8 oz. Tr. Digitalis (about 300 grains)	31F	None	Normal sinus rhythm	Nausea and vomiting; semistuporous	Atrioventricular dissociation, 170 auric rate, 66 ventricular rate, ST changes	Convulsions prior to demise	Died after 12 hours
Duvour, Pollet, Desolles, Gaultier ³	1938	6-8 mg. Digitaline Nativelle	52M	None	Normal sinus rhythm	Nausea, vomiting, amblyopia	Auricular fibrillation, 1st degree atrioventricular block and runs of nodal rhythm	Normal EKG 19 days later	Recovered
Duvour, Pollet, Desolles, Gaultier ³	1938	15 mg. Digitaline Nativelle	7F	Rheumatic mitral disease	Auricular fibrillation	Nausea, vomiting, pulsus bigemini, amblyopia, somnolence	Flutter fibrillation with ventricular premature; low voltage QRS	EKG still normal after 10 days	Recovered
Bickel, Plattner, Edelstein ⁴	1951	50 mg. Digitaline Nativelle	36F	None	Normal sinus rhythm	Vomiting, somnolence, blurred vision, hyperaesthesia, epigastric pain lasted 8 days	Normal sinus rhythm; variable atrioventricular block; A, and later, normal rhythm; ST changes	Normal EKG after 11 days, never exhibited ventricular irritability	Recovered
Vuletic, Ivancic ⁵	1952	5.8 gm. Digitaline Nativelle	50M	None	Normal sinus rhythm	Nausea, vomiting, cyanosis, conjunctival hemorrhages, epigastric tenderness, unresponsive hematuria	Sinus tachycardia; 2:1 atrioventricular block, 1st degree atrioventricular block; ST changes	EKG normal in 5 days	Recovered
Yu ⁶	1954	over 2.0 gm. Digitalis folia	42M	None	Normal sinus rhythm	Nausea, vomiting, abdominal cramps, diarrhea, basilar rales, apical systolic murmur, frequent premature contractions, pericardial rub, disorientation, confusion	Atrioventricular block; 2:1 anterior myocardial ischemia; bundle branch block; QRS 6.13		Recovered
This report	1954	7.5 mg. Digitalis toxin	61F	None	Normal sinus rhythm	Nausea, vomiting, basilar rales, grade I apical systolic murmur, irregular rhythm, palpable liver	Paroxysmal auricular tachycardia with atrioventricular block	Recovered from digitoxin	Died on 13th day from uremia, bronchopneumonia

Table 1 summarizes the reported observations of digitalis poisoning. Comparisons of the amount and type of drug, clinical effects and electrocardiographic manifestations are of particular interest. It is noteworthy that only one patient died of direct drug effect, and one other (ours) died of complicating disease.

In addition, another case, not reported in the literature, has been included through the kindness of Dr. Paul N. G. Yu, of Rochester, N. Y.⁶ Our case is presented to show serial electrocardiographic changes, metabolic responses and pathologic examination of the heart obtained at autopsy.

CASE REPORT

A 61 year old white woman was admitted to King County Hospital on March 25, 1954, with a history of having ingested 75 tablets of 0.1 mg. digitoxin in a suicide attempt eight hours previously. Two hours after ingesting the drug she had become nauseated and had vomited repeatedly, but no tablets were identified in the emesis.

Past medical history included an episode diagnosed as paranoid schizophrenia in 1941, and an admission to another hospital in 1953 for chest pain, hemoptysis, and

TABLE 2
Metabolic Observations

Balance Data*						Serum Electrolytes				
Hosp. Day	H ₂ O L.	Na mEq.	K mEq.	Cl mEq.	N gm.	Na mEq./L.	K mEq./L.	Cl mEq./L.	CO ₂ mEq./L.	BUN mg. %
0	-.83									21
1	+.43	-88	-96	-134	-2.3	137	6.2	109	24	43
2	-1.40	+66	-37	-44	-9.9	133	6.2	105	19	
3	-1.15	+26	-75	-132	-22.7					28
4	+0.37	-26	-50	-68	-18.5	139	5.0			32
5†								100	33	29
11	-.05	-3	-49	+62	-11.8	147	4.7	98	23	
12	+.95	-5	-77	+105	-18.4					105
13	+1.12	-5	-38	-29	-18.5	150	6.2	113	23	106

* Determined from measured intake and output, disregarding additional losses from specimens that were not saved.

† Cumulative weight loss, 4.0 kg.

Balance data are shown in the left half of the chart. Losses of water or electrolytes are indicated by minus signs, and gains by plus signs preceding the figure. Electrolyte quantities are all shown in milliequivalents. Nitrogen losses are recorded in grams per day. In the right half of the table, daily serum electrolyte concentrations are shown.

a consolidated left lower lobe. At this time there was no clinical evidence of heart failure, and an electrocardiogram was normal.

Physical Examination: The patient was a well developed and moderately alert white female who was retching violently. She was cooperative, but seemed apprehensive and expressed paranoid delusions. Blood pressure was 130/70 mm. of Hg; heart rate, 40; respirations, 20; rectal temperature, 100° F. The pupils were widely dilated but reacted to light and accommodation. There was minimal distention of the neck veins in the upright position. The thyroid was diffusely enlarged and was estimated to weigh 40 to 50 gm. The lungs were normal except for fine râles at the right costophrenic angle. The heart was slightly enlarged, with borders 10.5 cm. to the left of the midsternal line and 3 cm. to the right. The rhythm was grossly irregular. The apical heart sounds were diminished in intensity, and P₂ was slightly louder than A₂. A Grade 1 systolic murmur was heard along the left sternal border. The liver was palpable two fingerbreadths below the costal margin and was tender. There was no peripheral edema.

Laboratory Data: Hematocrit, 50%; white blood cell count, 17,800; erythrocyte sedimentation rate, 3 mm./hour (corrected). Kline test, negative. Urinalysis: specific gravity, 1.011; sugar, negative; albumin, negative; microscopic, negative. Blood urea nitrogen, 20.7 mg.%; CO_2 , 25; Cl, 109; Na, 137; K, 6.2 mEq./L. Subsequent changes in the electrolytes are summarized in table 2. The Decholin cir-

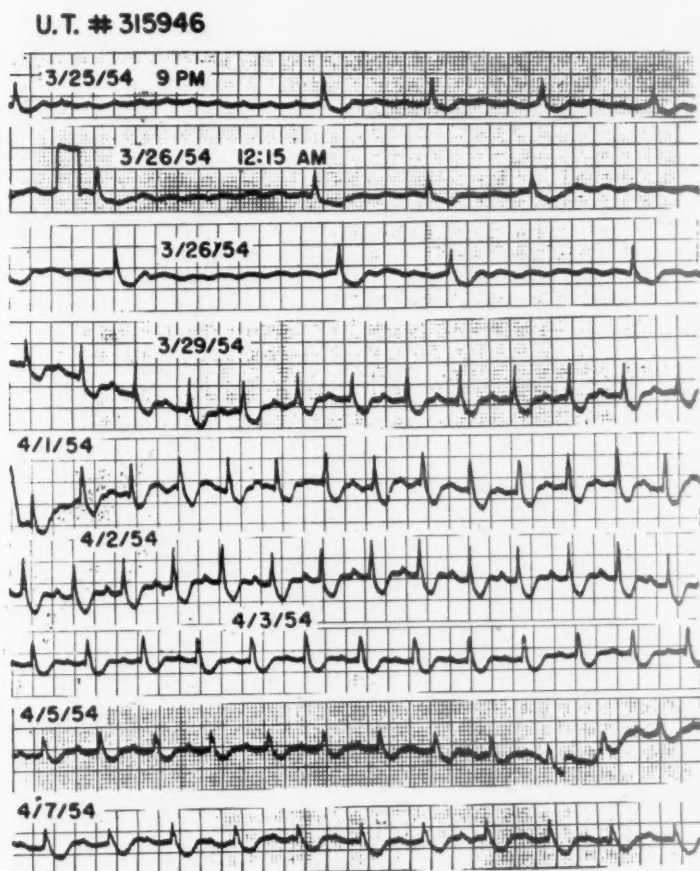


FIG. 1A. Serial recordings of electrocardiographic Lead II illustrate paroxysmal auricular tachycardia with 4:1 to 12:1 atrial ventricular block during the first two days. On March 29, 1954, there was a change to sinus rhythm with first degree atrial ventricular heart block; on April 2 the block disappeared, only to return three days later.

culuation time (arm-to-tongue) was 20 seconds; venous pressure, 90 mm. of H_2O ; vital capacity, 2.0 L.

Hospital Course: The patient was supported with oxygen by nasal catheter, and 5% dextrose in water intravenously, and then with Ringer's solution to which 20 mEq. potassium chloride were added. Two hours after admission there was a marked fall

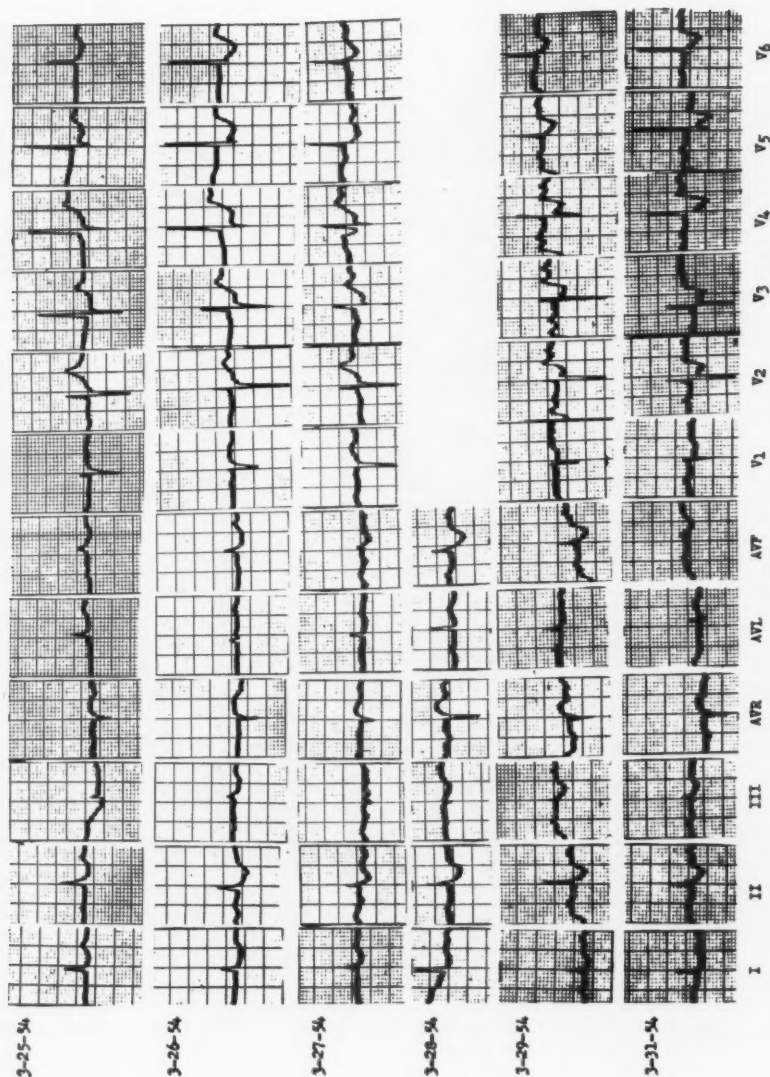


FIG. 1B.

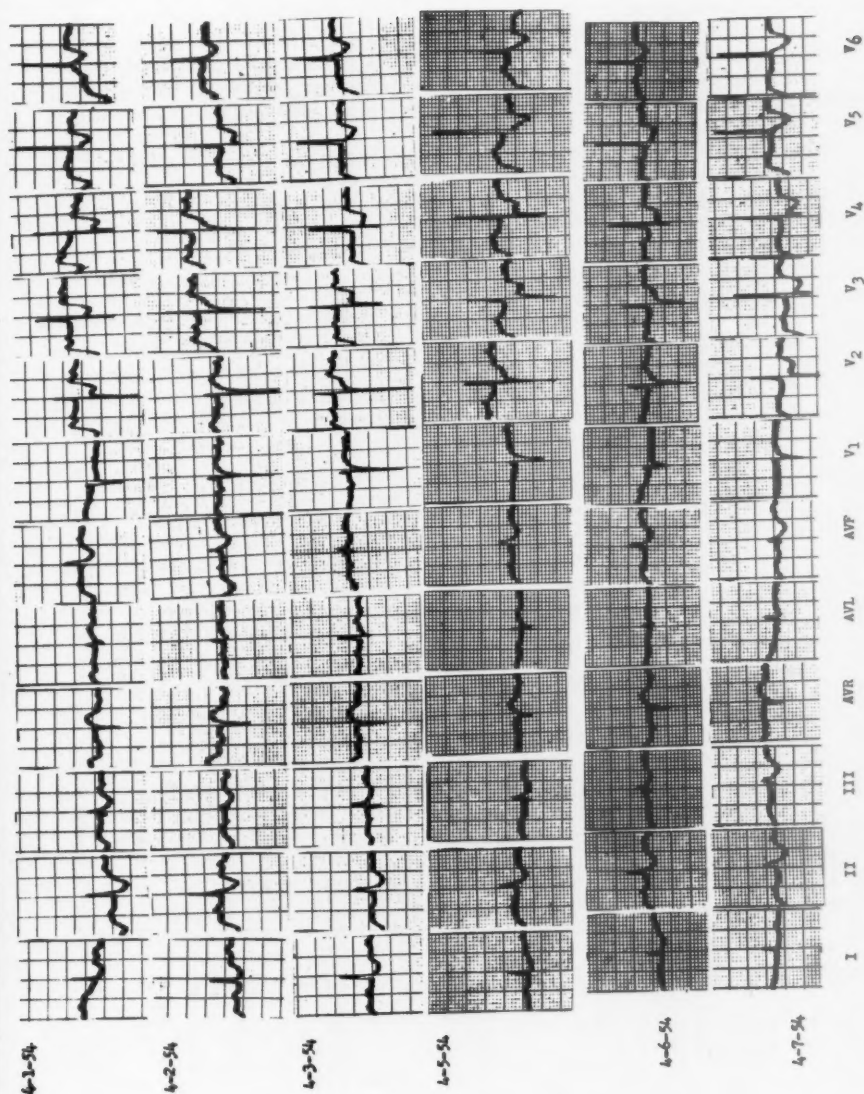


Fig. 1C.

FIG. 1B and C. Twelve lead electrocardiograms were made daily. This table includes daily specimens of each lead, grouped in columns to permit convenient comparisons of the ST-T changes. Note the remarkable ST segment depressions.

in the blood pressure, which was successfully treated by the addition of 4 mg. nor-epinephrine to the intravenous infusion. After 12 hours it was possible to discontinue pressoramine therapy.

The admission electrocardiogram showed paroxysmal atrial tachycardia, with A-V block ranging from 4:1 to 12:1 (figure 1A, 1B, 1C and table 3). This continued on the second day and, in addition, there were many ventricular premature systoles and one paroxysm, thought to be ventricular tachycardia, successfully treated with 400 mg. of Pronestyl intravenously.

The patient became quite drowsy. Retching continued but, with parenteral fluid therapy, urinary output was maintained. Circulation time declined to 10 seconds (arm-to-tongue) and remained at this level. No further potassium chloride was

TABLE 3
Serial Electrocardiographic Changes

Date	Day	AR	VR	AV Con- duction	PR	QT QT _c	ST-T Ele- vation aVR	ST Depres- sion V 3-4
3/25	0	240	40	4:1	—	40		
3/26 A.M.	$\frac{1}{2}$	230	38	12:1	—	.34 36	0.5	1
3/26 P.M.	1	230	38	4:1 8:1	—	.30	0.5	1.5
3/27	2	240	—	4:1	—	34	1.	2.5
3/28	3	—	—	—	0.28		2.5	
3.29	4	115	115	—	0.22	31 .43	2.5	2.0
3/30	5							
3/31	6						1.5	3.0
4/1	7	130	130		0.20	28 .41	2.0	5.0
4/2	8	125	125		0.16	24 .34	2.0	3.5
4/3	9	115	115		0.18	26 .36	2.0	2.5
4/4	10							
4/5	11	115	115		0.22	26 .36	1.5	4.0
4/6	12				0.19	30	1.5	3.0
4/7	13	100?	100		0.22	29 .37	1.0	2.0

Abbreviations:

AR = Atrial rate
VR = Ventricular rate
AV = Atrioventricular

PR = P-R interval
QT = QT interval, and QT_c signifies QT cor-
rected for heart rate

given in view of the serum level of 6.2 mEq./L. and rise of the blood urea nitrogen to 43.

On the third day more basilar râles and a 2 plus pretibial edema were noted. Drowsiness continued; the patient was disoriented and spoke in neologisms. The electrocardiogram showed paroxysmal atrial tachycardia with 4:1 A-V conduction.

On the fourth hospital day the cardiac mechanism returned to normal sinus rhythm with first degree A-V block. Emesis ceased, but oral feedings were refused. The patient became even more disoriented and withdrawn; the attending psychiatrist interpreted her behavior as a manifestation of acute toxic psychosis. An electroencephalogram revealed generalized symmetric high potential delta and theta activity

consistent with toxic delirium and clouded consciousness. The blood urea nitrogen had fallen to 32.

The situation remained unchanged until the eighth hospital day, when the patient developed a fever of 105° F. The urine for the first time contained clumps of white cells, and there was a leukocytosis of 50,200. Oxytetracycline therapy was begun, and the following day the temperature dropped to 100° F. and the patient was more responsive. However, the subsequent course was characterized by falling blood pressure, uremia and obtunded consciousness. A lumbar puncture revealed normal findings.

On the eleventh hospital day the patient had sudden onset of tachypnea, cyanosis and bubbling coarse râles throughout both lung fields. Blood pressure was 90/40 mm. of Hg; pulse, 160 (sinus tachycardia). Norepinephrine was administered, and a tracheotomy was done to permit aspiration of mucus. Her condition improved, but clinical and x-ray evidence of consolidation of the left upper lobe remained. An electrocardiogram showed a change to right axis deviation. A blood culture was negative, but urine culture revealed coli-aerogenes and proteus. In spite of penicillin and oxytetracycline therapy, the patient died three days later.

Metabolic Responses: The patient exhibited three phases with respect to her course in the hospital. Initially she was distressed almost continually by retching and profound nausea. From the fourth to tenth days there was a toxic delirium, during which time she refused oral feedings and was incontinent, so that balance studies were impossible. Finally, there was a febrile course associated with pyuria and azotemia.

The patient lost 4 kg. during the initial phase, despite efforts to replace fluid and electrolyte losses due to vomiting (table 2). As the urinary excretion of sodium and potassium decreased, the excretion of nitrogen increased markedly (to 22.7 gm. per 24 hours). Serum potassium rose to 6.2 mEq./L., and the CO₂ fell to 19 mEq./L. on the second day, but both returned to normal values thereafter.

The nitrogen excretion continued to be relatively marked during the third phase, as the blood urea nitrogen concentration increased to 106 mg.% on the thirteenth day.

AUTOPSY EXAMINATION

Cardiovascular System: The pericardium was normal. The heart weighed 385 gm.; there was no dilatation of any chamber. The valves were normal. The endocardium was smooth, glistening and tan colored, and there was no evidence of necrosis or hemorrhage in the subendocardial area. Myocardial thickness was 1 to 3 mm. in the right ventricle and 15 mm. in the left ventricle. The muscle tissues of the ventricular walls and papillary muscles were normal except for a few patches, 1 to 2 mm. in diameter, of tough gray tissue near the base of the interventricular septum. The coronary vessels and aorta were free of atherosclerotic plaques.

Thorax and Lungs: Firmly adherent, striated clots could be seen in many of the medium and small branches of the right pulmonary artery. In the left lung there were many semiconfluent areas of bronchopneumonia and focal atelectasis.

Gastrointestinal Tract: Unremarkable.

Liver, Biliary Tract, Pancreas: Normal.

Genitourinary: The left kidney weighed 240 gm. There was marked dilatation of the calyces and pelvis, and the mucosal surfaces were inflamed. The cortex and medulla were compressed, and the normal renal architecture was distorted. There was slight hydronephrosis on the right, but the corticomedullary architecture was essentially normal. The bladder showed acute cystitis.

Spleen: Multiple small infarcts.

Thyroid: A solitary, friable adenoma, 3.5 cm. in diameter, constituted the only visible gland tissue.

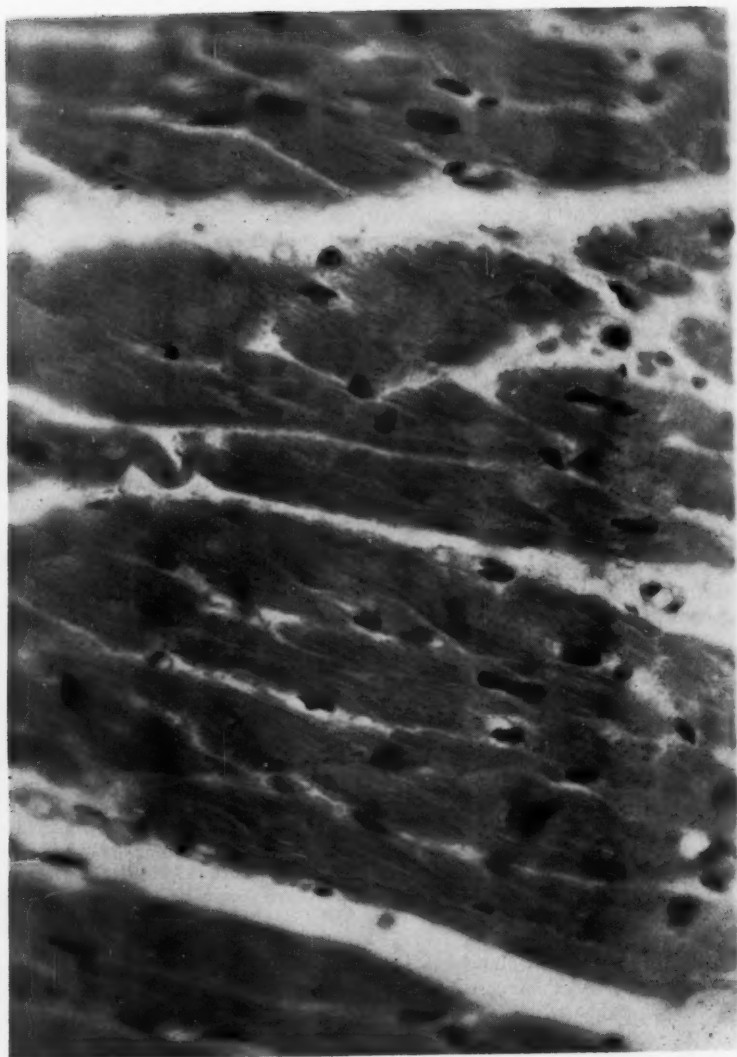


FIG. 2A.



FIG. 2B.

FIG. 2A and B. Two photomicrographs of the myocardium, A showing no abnormality, B showing one of the rare areas where there was a little intercellular edema and a slight increase in the number of interstitial cells.

MICROSCOPIC EXAMINATION

Heart: Interventricular septum: Arteriosclerotic changes in a few vessels. Fibrinoid necrosis in the intima and media of a few vessels. Small mural thrombus with secondary suppuration, undergoing organization.

Left ventricle: Some perivascular fibrosis of mild degree. There was perhaps a little increase in the number of interstitial cells, and the capillaries were a little more prominent than normal. There was some suggestion of intercellular edema of mild degree.

Right ventricle: Normal.

Inter-atrial septum: Fatty infiltration.

Atrial wall: Mild interstitial fibrosis.

Atrial appendage: There was a little interstitial hemorrhage.

Aorta: Normal.

Impression: An essentially normal heart for this age (figure 2 A and B).

Lung: Multiple sections revealed a varying picture, including hyperemia, edema, intra-alveolar fibrin, hemorrhage and masses of polymorphonuclear leukocytes. The bronchioles were filled with polymorphonuclear leukocytes.

Kidney: Right: Aside from congestion, an unremarkable kidney.

Left: The capsule was thickened, and there were some hyalinized glomeruli. Congestion was generalized, there were lymphocytic infiltrates and mild arteriosclerotic changes. Some tubules contained eosinophilic hyaline material, and their lining was attenuated.

Impression: Compatible with hydronephrosis.

Liver: A mildly congested, minimally fatty liver.

Adrenal: Congestion of the cortex, especially in the zona reticularis.

Pancreas: There was spotty intralobular fibrosis of a very mild degree, and some dilatation of acini.

DISCUSSION

In spite of the massive dosage of digitalis glycoside ingested, no specific cardiac damage could be identified at autopsy. We know of no previous reports of histologic examination of the human heart shortly after a massive overdose of digitalis, and earlier reports do not give a clear idea of what might be expected. Dearing⁷ found subendocardial and posterior papillary muscle necrosis and hemorrhages in cats given digitalis leaf or pure crystalline preparations orally or parenterally, whereas La Due⁸ found such lesions in the dog only after parenteral administration. Travell⁹ also observed such lesions in cats following parenteral administration, but found no cardiac hemorrhages in humans who had received large oral doses of digitalis for varying periods prior to death.

Lown and Levine¹⁰ have stated that patients with paroxysmal auricular tachycardia with block due to digitalis usually have serious underlying heart disease, yet none was found in this patient; and although the electrocardiogram showed an ST-T pattern which might be interpreted as myocarditis, ischemia or even subendocardial infarction, no autopsy confirmation was found for any of these. Obviously this does not exclude the possibility that minute changes might have been demonstrable by other methods.

The magnitude of the nitrogen loss (22.7 gm.) observed in this patient on the third day prior to her infectious complications was probably related to the digitoxin poisoning, although this cannot be stated with certainty. Attention is drawn to this observation with the hope that it may be investigated in any

future cases of massive poisoning from digitalis or its derivatives. The relationship of this marked renal excretion of nitrogen to the toxic delirium was not established.

In view of the drastic consequences usually expected of digitalis poisoning, it is encouraging that the death of only one of the eight cases reviewed was due to direct drug action.

SUMMARY

Paroxysmal auricular tachycardia with A-V block was observed in a 61 year old patient without previous heart disease who ingested 7.5 mg. of digitoxin with suicidal intent. The usual manifestations of profound nausea and vomiting were observed, as well as a toxic delirium and an excessive renal excretion of nitrogen. Although death occurred, it was on the thirteenth day and was due to bronchopneumonia and uremia rather than to cardiac effects. No significant myocardial changes were observed at autopsy.

The mortality rate determined in a review of cases of acute massive digitalis poisoning was found to be 13%.

SUMMARIO IN INTERLINGUA

Le opportunitate de observar le responsas myocardial e metabolic a invenenamento per digitoxina esseva providite per un femina de 61 annos de etate qui ingereva 7,5 mg de digitoxina in le tentativa de suicidar se. Octo horas plus tarde illa habeva un attacco violente de vomiturition e se trovava in un stato delusional. Le examine del corde revelava un rhythmo grossiermente irregular que esseva identificate per le electrocardiogramma como paroxysmal tachycardia atrial con bloco atrioventricular variabile (4: 1 a 12: 1). Iste rhythmo persisteva durante tres dies e esseva reimplaciate per normal rhythmo sinusal con bloco atrioventricular del prime grado. Post octo dies il non habeva bloco cardiac, sed duo dies ante morte le intervallo P-R se augmentava a 0,22 secundas. Studios metabolic revelava inexpectatemente alte niveles del excretion de nitrogeno. Le patiente moriva le dece-quarte die con bronchopneumonia, pyuria, e azotemia.

Examines macro- e microscopic del corde resultava in essentialmente normal constataiones, viste le etate del patiente. Bronchopneumonia e atelectasis focal esseva trovate in le pulmon sinistre. Multe parve embolos esseva trovate in le pulmon dextere. Le ren dextere esseva normal; le ren sinistre esseva hydronephrotic.

Patientes con paroxysmal tachycardia atrial con bloco producite per digitalis ha usualmente serie subjacente morbos cardiac. In le patiente del presente reporto, le electrocardiogramma revelava configurationes ST-T que on poteva interpretar como myocarditis, ischemia, o infarcimento subendocardial, sed nulle anormalitate anatomic esseva trovate al necropsia.

Le revista del litteratura produceva solmente septe altere casos de invenenamento per doses massive de glycosidos de digitalis. In solmente un de iste casos esseva le morte le effecto directe del droga. Viste le consequentias drastic que es usualmente expectate ab dosages excessive de digitalis, le facto que il existe solmente un previe reporto de morte como effecto del droga es incoraggiante.

BIBLIOGRAPHY

1. Tomazewski, D. W., and Lapa, D. W.: Un cas d'intoxication digitale, Arch. d. mal. du coeur 29: 196, 1936.
2. McGuire, J., and Richards, C. E.: Fatal digitalis poisoning occurring in a normal individual, Am. Heart J. 12: 109, 1936.

3. Duvoir, M., Pollet, L., Desoille, H., and Gaultier, M.: Deux cas d'intoxication par la digitaline. *Etude electrocardiographique*, Bull. et m  m. Soc. m  d. d. h  p. de Paris **54**: 159, 1938.
4. Bickel, G., Plattner, H., and Edelstein, H.: Intoxication digitalique massive terminie par la gu  rison, *Arch. d. mal. du c  ur* **44**: 61, 1951.
5. Vuletic, V., and Ivancic, R.: A propos d'un cas d'intoxication aigue et massive par la digitale, *Arch. d. mal. du c  ur* **45**: 853, 1952.
6. Yu, P. N. G.: Personal communication, 1954.
7. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments with calculated therapeutic and toxic doses of digitalis. I. Effects on myocardial cellular structure, *Am. Heart J.* **25**: 648, 1943.
8. La Due, J. S.: Myocardial necrosis and fibrosis resulting from the administration of massive doses of a cardiac glycoside, *J. Pharmacol. and Exper. Therap.* **76**: 1, 1952.
9. Travell, J., Gold, H., Modell, W., and Auerbach, O.: Study of cardiac hemorrhages caused by digitalis glycosides, *Federation Proc.* **1**: 170, 1942.
10. Lown, B., and Levine, S. A.: Current concepts in digitalis therapy. Part II, *New England J. Med.* **250**: 819, 1954.

AN UNUSUAL SOURCE OF RECURRENT PULMONARY EMBOLI: PRIMARY PELVIC VARICOCELE *

By SEYMOUR B. LONDON, M.D., and ROSE E. LONDON, M.D.,
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PULMONARY thrombo-embolic disease, because of its frequency and serious implications as a cause of morbidity in the aged and the chronically ill, and in postoperative states, has received increasing clinical attention. In the young, noncardiac, nontraumatized healthy individual, however, recurrent pulmonary embolization is a relative rarity. We recently treated a 40 year old housewife who, over a 10 year period, suffered more than 100 episodes of pulmonary embolization of undiagnosed origin. The diagnosis of pelvic varicocele was eventually established, and the patient was treated and cured by vena caval ligation and surgical excision of the source of the emboli.

Our object in reporting this case is to call attention to primary pelvic varicocele as a source of thrombo-embolic phenomena in an otherwise healthy young female.

CASE REPORT

A 40 year old housewife entered the Mt. Sinai Hospital, Miami Beach, Florida, on February 3, 1953, with the chief complaint of pain in the left chest of three days' duration. She had been in good health until the age of 31, when she first developed the sudden onset of pleuritic pain in the left chest which lasted approximately eight to 12 hours. Subsequently she experienced over 100 similar episodes, usually involving the left chest and occasionally the right. Eighteen months prior to admission,

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during an episode of chest pain, the patient developed a hemorrhagic pleurisy. A presumptive diagnosis of bilateral phlebothrombosis was made and a bilateral femoral vein ligation was done at another hospital. Despite this, the patient continued to have episodes of chest pain approximately every four to six weeks. In addition, eight months of Dicumarol therapy, with the prothrombin time maintained between 21 and 33 seconds, failed to alter the severity or frequency of the episodes. Because of the terrifying nature of each attack and the dread of the anticipated recurrences, this woman led the life of a chronic invalid for 10 years. During the week prior to

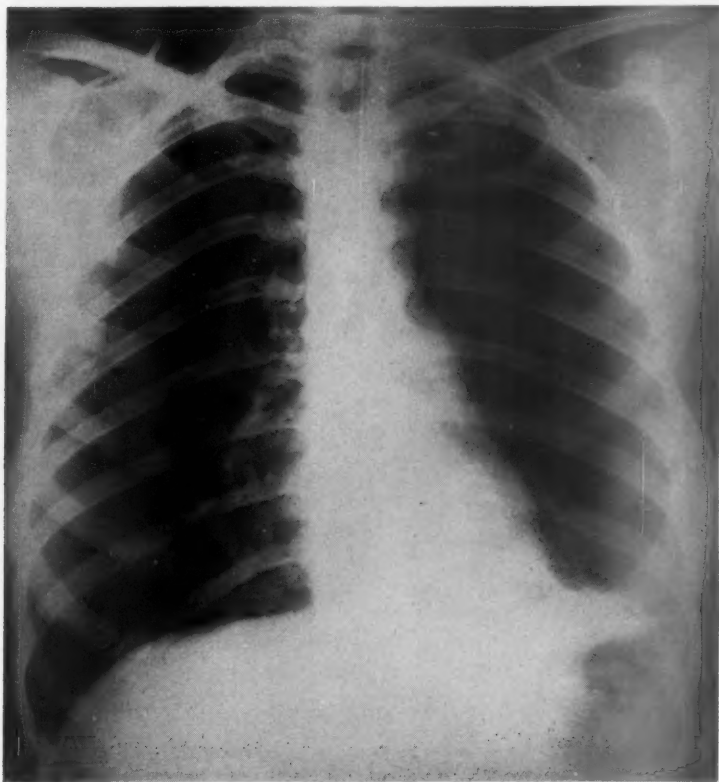


FIG. 1. Chest x-ray on day of admission, showing small area of consolidation at left base.

admission the patient had three very severe episodes of chest pain, twice on the left side and once on the right, which required narcotics for relief and were associated with a feeling of impending disaster. There had never been associated hemoptysis, cough or expectoration, nor was there history of nausea, vomiting, abdominal pain, melenä or bloody stools. No history of dysuria, hematuria, pyuria, nocturia or frequency was elicited. The menstrual periods were painful and irregular, occurring approximately twice monthly. During the five to six months prior to admission the patient had had menorrhagia. There was a past history of jaundice at the age

of 10, and an appendectomy at the age of 20. A single pregnancy resulted in a stillborn child. There was no history of pneumonia, pleurisy, malaria, typhoid, rheumatic fever, tuberculosis, allergy or diabetes. The family history was noncontributory.

Physical examination revealed a 40 year old white female who appeared acutely ill. The skin showed no eruptions, petechiae or purpura. The skull was symmetric. The pupils were equal and responded well to light and accommodation. There was no nasal obstruction and no nasal discharge. The mouth and pharynx

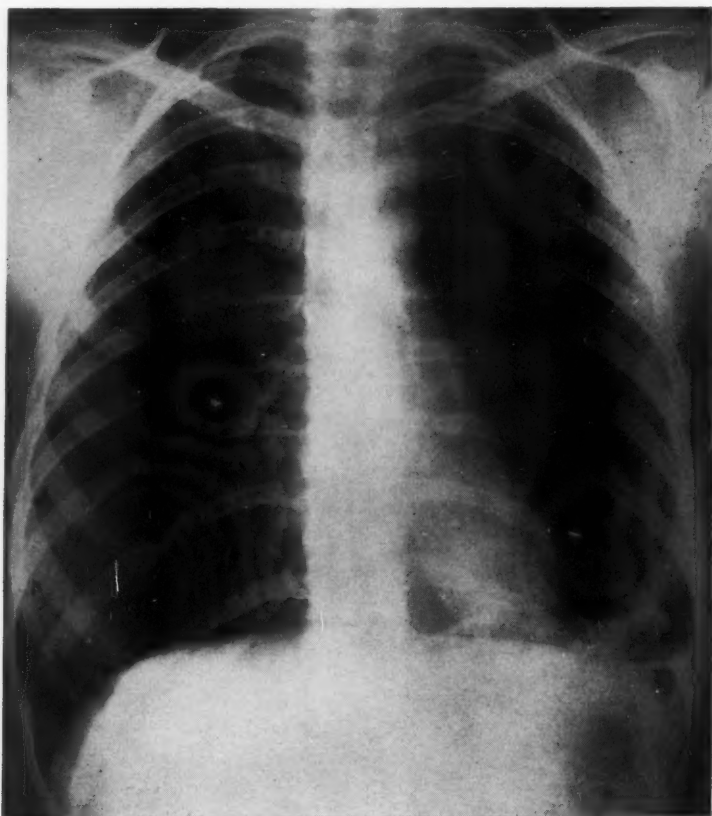


FIG. 2. Chest x-ray on third day after admission, showing regressive changes of pulmonary infarction.

were normal. The chest was symmetrical. Diminished breath sounds were heard over the left lower lobe, but no râles were audible. The heart was not enlarged. There was a regular sinus rhythm, and no murmurs were heard. The blood pressure was 110/70 mm. of Hg. The abdomen was soft and symmetrical and no masses or organs were palpable. There was some percussion tenderness over the left costal margin posteriorly. Pelvic examination revealed a mucopurulent vaginal discharge.

The cervix was clear, but there was some reddening of the vaginal wall. The uterus was slightly nodular on the anterior surface. There was tenderness in both adnexal areas, with a sensation of soft, cordlike masses bilaterally. The extremities showed no edema, alteration in pulsations, Homans' sign or calf tenderness.

X-ray of the chest (figure 1), taken shortly after admission, revealed a small, irregular area of consolidation at the extreme left base posteriorly, with an associated elevation of the diaphragm and obliteration of the posterior costophrenic sulcus. A repeat examination (figure 2) two days later revealed the area of consolidation

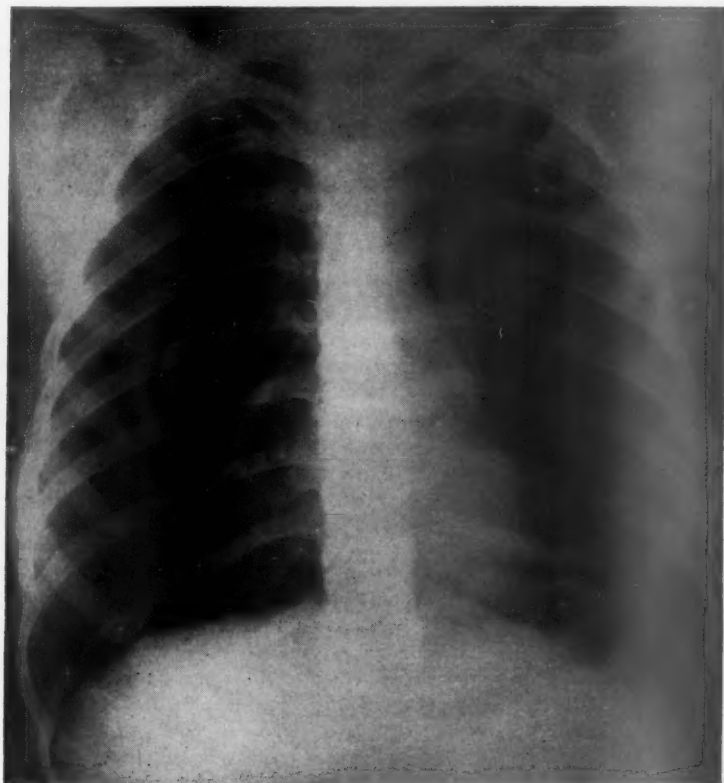


FIG. 3. Chest x-ray two weeks later, showing complete clearing.

previously visualized to have diminished slightly in size, and two weeks later (figure 3) the density had completely cleared. An intravenous pyelogram revealed no abnormalities except for the presence of phleboliths. An electrocardiogram revealed an essentially normal tracing. Laboratory examination of the urine was normal. The hemogram on admission revealed a leukocytosis of 17,500, with a red blood count of 4,100,000 per cubic millimeter; hemoglobin, 12 gm. per 100 c.c., and a percentile differential of polymorphonuclears, 49; bands, 9; lymphocytes, 35; monocytes, 6; eosinophils, 1. Platelets were normal (407,000 per cubic millimeter). The cor-

rected sedimentation rate was 13 mm. per hour. Blood chemical tests per 100 c.c. blood were: uric acid, 1.6 mg.; calcium, 10.5 mg.; phosphorus, 3.3 mg. The alkaline phosphatase was 2.0 Bodansky units; icteric index, 7.05; blood coagulation time, normal. An L.E. cell preparation was negative. The cephalin flocculation was 1 plus in 24 hours and 2 plus in 48 hours.

Because of the presumptive diagnosis of multiple pulmonary emboli originating in the pelvis, a 10 day course of anticoagulant therapy was followed by abdominal surgical exploration. At surgery the spectacular finding was the presence of tremendous varicosities of the broad ligament and ovarian veins, filling the pelvis and extending up to the inferior vena cava and left renal vein. The uterus was moderately enlarged due to fibromyomata. The vena cava was dissected free and ligated, and the broad ligament, containing the mass of dilated veins, was removed; in addition, a supravaginal hysterectomy and bilateral salpingo-oophorectomy were done. The ovarian pedicles were excised and ligated bilaterally. Pathologic examination of excised veins failed to show either thrombi or perivascular inflammation of the dilated veins.

The patient had an uneventful postoperative convalescence and was discharged nine days later. Following surgery, anticoagulant therapy was instituted and maintained for six weeks. Until the time of this writing, 30 months postoperatively, the patient has remained in completely good health, with no evidence of recurrence.

DISCUSSION

Stimulated by the unusual finding of pelvic varicocele as a cause of pulmonary thrombo-embolism, we reviewed the literature and were impressed by the paucity of reports on the subject of pelvic varicocele.^{1, 2, 3} The ovarian veins, after leaving the ovary, pass between the layers of the broad ligament, forming a freely anastomosing pampiniform plexus with tributaries from the fallopian and uterine veins. From the plexus two veins issue, which finally fuse into a single terminal ovarian vein. The vein from the left side empties into the renal vein at a right angle, that from the right, directly into the inferior vena cava. As in the analogous situation of spermatic varicocele in the male, the pampiniform plexus may become dilated and tortuous, to form a pelvic varicocele, and aneurysmal dilation of the veins of the broad ligament. It is possible that the absence of valves in this plexus predisposes to the distention of the veins. Although this condition is bilateral, left varicocele is more prominent in both male and female, presumably because of the circuitous venous return on the left.

Pelvic varicocele may be a secondary manifestation of abnormalities in the pelvis, such as pelvic inflammatory disease, retroversion of the uterus, venous obstruction by masses or tumors, and venous stasis as seen in heart disease. Primary pelvic varicocele as seen in healthy young females must be considered to be of unknown etiology and is a relatively rare condition, if one can judge from the few and scattered reports in the Spanish, French, Italian and American literature.^{1, 2, 3, 4} It has been suggested that it is a congenital or developmental anomaly of the walls of the veins.

The recognition of pelvic varicocele is difficult clinically. The symptoms, often slight and nonspecific, are lower abdominal and pelvic pain or a feeling of pressure in the pelvis, aggravated by standing and relieved by lying. Intensification of symptoms may occur prior to menstrual periods and may be associated with other menstrual disturbances, such as menorrhagia and metrorrhagia.

The physical findings are meager. The uterus may be slightly enlarged, tender or retroverted. Careful palpation may reveal soft, cordlike masses in the adnexae. This is more apparent when the patient is in the standing or semi-recumbent position.⁴ X-ray of the pelvis may reveal phleboliths, the small calcified remnants of pelvic thrombi.⁵ During pregnancy, rupture and retroperitoneal hemorrhage from one of these vessels occasionally but dramatically call attention to this syndrome.⁶

While it has been reported that thrombi may occur in pelvic varicocele in the female, it has not been generally recognized that embolization may occur, and we have been unable to find another report of thrombo-embolic disease secondary to pelvic varicocele. Our case is notable not only for thrombo-embolic disease but also for the numerous, nonfatal emboli occurring well over 100 times during a 10 year period. The pattern of repeated pulmonary embolization, despite prior femoral vein ligation and adequate anticoagulant therapy, forced us to reconsider the pelvic veins as the origin of the thrombi. The palpation of soft but definite cordlike structures in both adnexal areas confirmed our suspicion of venous pathology. Exploratory laparotomy revealed a spectacular mass of dilated veins, spreading out in both broad ligaments and extending up both ovarian veins. Pathologically these veins failed to show either thrombi or inflammatory changes, and it is conjectured that distortion of the veins resulted in sufficient stagnation of the circulation to give rise to repeated, nonadherent thrombi. Presumably these were of small caliber, since, contrary to the expected mortality rate, the patient survived more than 100 episodes.

While the usual treatment for pelvic varicocele is local excision,^{3,4} in our case the pathology was so extensive that fear of dislodging a large thrombus during surgery prompted the ligation of the inferior vena cava prior to manipulation of the pelvic contents.

The uneventful recovery of this patient and the continued good health for a period of 30 months (up to the present time) are in marked contrast to the previous 10 years of invalidism.

CONCLUSION

1. An unusual case is presented of thrombo-embolic disease arising from primary pelvic varicocele, with over 100 pulmonary emboli in a 10 year period, in an otherwise healthy young woman.
2. Removal of the pelvic varicocele and inferior vena cava ligation resulted in complete cure of the condition.

SUMMARIO IN INTERLINGUA

Es reportate le caso inusual de un menagera de 40 annos de etate, alteremente in bon stato de sanitate, qui experienciava plus que 100 episodios de embolismo pulmonar in le curso de un periodo de 10 annos. In despecto de bilateral ligation femoral e un prolongate therapia anticoagulante, le episodios recurreva a intervallos de quatro a sex septimanas, resultante in un stato de invaliditate. Al tempore de nostre examine, le presentia de sensible massas de forma tendinose in ambe areas adnexal induceva nos a effectuar un laparotomia exploratori. Isto revelava numerose enorme varicositates del large ligamentos e del venas ovarian. Ligation del vena cave inferior esseva combinate con le excision del large ligamentos, hysterectomia supravaginal e

bilateral salpingo-oophorectomia. Iste manovra resultava in le complete cura del patiente qui ha remanite in bon stato de sanitate usque al tempore del redaction de iste reporto (30 menses plus tarde).

Le pertinente aspectos clinic de varicositates pelvic o varicoceles es discutite. Ben que varicositates in le pelve es vidite frequentemente como sequella de conditiones pathologic del pelve (per exemplo tumor, inflammation, o stasis venose), le occurrentia de primari varicoceles pelvic in un juvene feminina de bon sanitate es rar e de etiologia incognoscite. Nostre revista del literatura ha revelate nulle altere caso de recurrente embolismo pulmonar effectuate per varicoceles pelvic. Tamen, proque iste condition pote esser curate per medios chirurgic, le possibilitate de variocoles pelvic debe esser prendite in consideration in patientes feminin con thrombo-embolismo de origine incognoscite.

BIBLIOGRAPHY

1. Fegerl, H., and Narik, G.: Die Varicocele pelvina muliebrum als selbstaendiges Krankheitsbild (varicocele pelvina muliebrum as an independent entity), *Zentralbl. f. Gynäk.* **76**: 392, 1954.
2. Imparato, E.: Il varicocele pelvico, *Rassegna internaz. clin. e terap.* **32**: 628, 1952.
3. Ferreira Gomez, A.: Chronic pelvic congestion in female; importance of gynecologic varicocele, *Rev. españ. obst. y ginec.* **10**: 347, 1951.
4. Davis, C. H.: *Gynecology and obstetrics*, edited by Davis, C. H., and Carter, B., 1953, W. F. Prior Company, Inc., Hagerstown, Maryland, Vol. 2, Chapter 18, p. 43; Vol. 3, Chapter 18, p. 207.
5. Crossen, H. S., and Crossen, R. J.: *Diseases of women*, 9th Ed., 1944, The C. V. Mosby Company, St. Louis, p. 656.
6. Hodgkinson, C. P., and Christensen, R. C.: Hemorrhage from ruptured uteroovarian veins during pregnancy; report of 3 cases and review of the literature, *Am. J. Obst. and Gynec.* **59**: 1112, 1950.

MYXOMA OF THE LEFT ATRIUM: REPORT OF A CASE *

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MYXOMA of the heart has been diagnosed before death only on rare occasions; indeed, this disorder is usually mistaken for mitral stenosis.^{1, 2, 3, 4, 5, 6, 12} Because of the difficulty in arriving at a correct clinical diagnosis, it is believed that individual case reports are warranted, particularly in view of recent advances in cardiac surgery which make resection of such tumors possible.

Atrial myxoma usually produces a diastolic rumble at the apex identical with that of mitral stenosis. Review of the literature suggests that when rheumatic mitral stenosis is suspected, certain atypical features might suggest atrial tumor: (1) marked alteration in the character of the mitral murmur when the patient's position is changed; (2) extreme respiratory embarrassment resulting from certain changes in body position;⁶ (3) syncope occurring with change in body position rather than exercise; (4) substernal pain, palpitation, edema and dyspnea disproportionate to the degree of atrial enlargement or intensity of the

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murmur.¹ Other clinical features of this disorder include rapid progression, unresponsiveness to digitalis, development of angina,⁵ low systolic blood pressure,⁵ conduction defects, atrial arrhythmias and peripheral embolization.^{1,3} Sudden death may occur when the tumor blocks the mitral orifice.

CASE REPORT

The patient, a 54 year old white housewife, had a history of several previous illnesses which we suspect may have coexisted with the malady that led to her death. In 1940 a right radical mastectomy was performed because of adenocarcinoma. No distant metastases were found. In 1948 a subtotal thyroidectomy was performed, with removal of a nontoxic, benign nodular goiter. In 1951, because of a cystoma of the left ovary, a total hysterectomy with bilateral salpingo-oophorectomy and appendectomy was performed. In 1951 the patient underwent a second tonsillectomy. In April, 1952, the patient was admitted to Midland Memorial Hospital with a temperature of 102° F. No abnormal physical findings were recorded. Roentgen films of the chest revealed a small area of finely mottled infiltration in the right midlung field; otherwise the lung fields were clear. The heart and great vessels were within normal limits. The absence of the right breast shadow was noted. The bony thorax was normal, and it was thought that the mottled infiltration in the right midlung field represented a small area of pneumonia. The hemoglobin was 12 gm.; white blood cells, 14,900, with a normal differential. After 48 hours of observation the patient was discharged afebrile. In October, 1953, a hemorrhoidectomy was performed. Examination of the blood prior to surgery revealed a hemoglobin of 11.57 gm., 3,850,000 red blood cells and 7,800 white blood cells, with a normal differential. On February 3, 1954, the patient was re-admitted to Midland Memorial Hospital with symptoms of chest cold, low grade fever with evening rise to 101° F., and mild cough productive of a small amount of clear phlegm. Physical examination revealed normal lung findings. There were no cardiac murmurs at rest, after exercise, or after the patient was placed in the left lateral recumbent position. The chest films revealed a suggestion of enlargement of the hilar lymph nodes, especially on the left. There was also some increased prominence of the pulmonary markings about the left lower lung field. The value for hemoglobin was 10.5 gm. per 100 c.c. of blood. The erythrocyte count was 3,150,000 and the sedimentation rate 45 mm. in one hour (Wintrobe method). The direct Coombs' test was negative. Hematocrit was 38.2 vol.%. Blood cultures were sterile. Total serum protein was 8.14 gm.%; albumin, 5.94 gm.; globulin, 2.2 gm.; alkaline phosphatase, 3.28 Bodansky units. Roentgenographic study of the colon and a sigmoidoscopy revealed no abnormalities. The course in the hospital was uneventful and the patient was discharged unchanged after five days of observation.

On February 26, 1954, the patient was re-admitted to the hospital. The symptoms were essentially the same as on previous admission, and physical examination showed no change. Three blood cultures remained negative. The hemoglobin measured 9.8 gm. per 100 c.c. of blood. The erythrocytes numbered 3,200,000 and the leukocytes 9,200, with a normal differential. An agglutination series for febrile diseases was negative, as was a Wassermann test. Urinalysis was normal. An excretory urogram revealed that the kidneys, ureters and bladder were normal. The serum calcium level was 9.12 mg.%. Phosphorus was 3.6 mg.%. The patient ran a low grade fever (between 100 and 101° F.) during the entire hospital stay. Finally, after one month of observation, she was discharged with a diagnosis of fever of unknown cause.

From March, 1954, to October, 1954, the patient received two blood transfusions

to combat the unexplained anemia. Her weight declined several pounds. She became somewhat dyspneic on exertion and took a course of antamebic medication (chloroquine), which was ordered following an evaluation in another medical center.

On October 20, 1954, the patient was re-admitted to Midland Memorial Hospital with symptoms of weakness and of progressive dyspnea on slight exertion. The hemoglobin measured 10.13 gm. per 100 c.c. of blood. The erythrocytes numbered 3,500,000 and the leukocytes 9,500, with a normal differential. Roentgenographic examination of the chest revealed definite bilateral hilar lymphadenopathy and a fine interstitial infiltration extending out from both hilar regions into the periphery of the lung field, more marked on the left. There was a small amount of pleural fluid at the left base and a beginning widening of the left perivertebral line in the lower portion of the mediastinum, which could represent tumor or fluid. An electrocardiogram revealed low voltage and right axis deviation. Circulation time (Decholin sodium) was 17 seconds, vital capacity was 2 L. (60% of normal). Interval films on December 28, 1954, revealed continued increase in the bilateral interstitial infiltration and continued hilar enlargement. There was now some fluid at the right base also, while that at the left base had decreased. The transverse cardiac diameter had slowly increased, with straightening of both cardiac borders. This change was compatible with widespread mediastinal malignancy, and suggested possible invasion of the pericardium.

On the basis of clinical, roentgenologic and electrocardiographic observation, a diagnosis of lymphatic spread of metastatic carcinoma throughout both lung fields, originating from adenocarcinoma of the right breast, was entertained. Testosterone, 50 mg. three times a week, was injected for four weeks, without improvement. Other possibilities were thought to be collagen disease or progressive subacute interstitial pulmonary fibrosis (Hamman-Rich syndrome). In the absence of lymph nodes or other suitable biopsy material, lung biopsy was attempted. However, the patient immediately went into shock upon administration of anesthesia and the thoracotomy was abandoned. After 38 days of observation the patient, now bedridden, was allowed to return to her home. Medication consisted of gitalin, 0.5 mg. daily, and thyroxin, 0.1 mg. daily.

About five weeks after leaving the hospital the patient was re-admitted on January 4, 1955, because of progressive dyspnea, both exertional and at rest, mild orthopnea and increasing weakness. She had also noted progressive dependent edema of ankles, legs, thighs, hips and presacral area. The abdomen had become moderately enlarged and tense, with occasional mild, cramping pains. The blood pressure was 112/74 mm. of Hg; pulse, 92; temperature 98.8° F. There was jugular vein distention bilaterally with the patient in the upright position. There was diminished expansion of the chest bilaterally. There were bronchial breath sounds throughout both lung fields, moist râles in both bases, and no significant change in fremitus. When the heart was examined the point of maximal impulse was found in the anterior axillary line, diffuse but strong. The sounds were loud and of good intensity. Again, no cardiac murmurs could be heard, even in the left lateral recumbent position. P_2 was louder than A_2 . Venous pressure measured 133 mm. of water. Circulation time, arm-to-tongue, was 40 seconds; this was considered to be the result of intrapulmonary obstruction. The abdomen was moderately distended, with almost generalized dullness to percussion. Some definite shifting dullness and fluid were noted, and the liver edge was about 4 cm. below the right costal margin. The surface was smooth and moderately tender. Three plus edema of the entire lower extremities was noted. Electrocardiographic examination revealed right axis deviation and digitalis effect. Chest fluoroscopy showed minimal changes in the appearance of the extensive pulmonary infiltration in both lungs, and cardiac enlargement was more prominent.

The patient's condition deteriorated gradually and steadily. Râles appeared in increasing numbers; intractable cough, dyspnea and orthopnea persisted. Abdominal distention increased, the edema of the legs became more marked, and there was progressive, severe prostration. Periods of stupor developed and deepened gradually



FIG. 1. Cross specimen of heart, showing origin of tumor on interatrial septum of left atrium.

to terminal coma. Death occurred on the eighteenth day following admission to the hospital.

Autopsy: At autopsy the heart weighed 323.5 gm. The pericardium was smooth. No increase in pericardial fluid was found. The coronary vessels were patent and normal in appearance. When the heart was opened the following measurements were

established: thickness of left atrium, 1.5 to 2 mm.; thickness of right atrium, 1.0 to 1.5 mm.; thickness of left ventricle, 2.0 to 6.0 mm.; thickness of right ventricle, 2.0 to 5.0 mm.; circumference of aortic valve, 2.8 cm.; circumference of pulmonary valve, 2.5 cm. The left atrium contained a lobulated grayish tumor mass (figure 1) measuring 5.5 cm. in length by 4 cm. in width by 1.2 cm. at the base. The base of the tumor was attached to the upper edge of the foramen ovale, which was anatomically patent but physiologically closed. On cut surface the tumor had a gray-yellow color, with evidence of numerous old and recent hemorrhagic areas. Inspection of the valves revealed no abnormalities. The remainder of the endocardium was slightly thickened. In general, the myocardium appeared somewhat pale.

Inspection of the lungs showed marked edema and congestion throughout. The trachea and bronchi contained a large amount of foamy, pale-staining fluid. No consolidation in the parenchyma of the lungs was found. There was fibrosis in the subpleural area of the lower portion of the right upper lobe. The tracheobronchial lymph nodes were only slightly enlarged, and appeared soft and gray in color on cut surface. Lymph nodes taken from the left axilla showed similar characteristics.

Histology: The lungs showed evidence of chronic passive hyperemia. There were thickening of the alveolar septa and desquamation of numerous endothelial cells which were loaded with hemosiderin (so-called "heart failure" cells). In other areas many alveoli were noted which were filled with an acellular exudate suggesting the presence of pulmonary edema. Foci of emphysema were present throughout all sections.

Section from the tumor of the heart revealed that it had arisen from the wall of the left atrium, as manifested by the blending of the tumor and myocardial tissue. At the base of the tumor there was heavy fibrosis with formation of cartilage and even some calcification. In these areas there was also evidence of old hemorrhage, with deposition of much hemosiderin. In the periphery, the tumor formed a loose network of elongated, spindle-shaped cells. Between the cells there was a matrix of homogeneous, metachromatic material suggesting the presence of large amounts of mucin.

The section from the liver showed evidence of chronic passive hyperemia, which was manifested by engorgement of the central veins and the sinusoids leading to the central veins. Many of the sinusoids had ruptured, producing zones of hepatic necrosis in the center of the liver lobules. Hemosiderin deposits were common, suggesting that the process was not of recent origin.

Sections from the remaining organs were not remarkable. There was no evidence of metastasis from breast carcinoma.

COMMENTS

No evidence was found to indicate that this tumor-bearing heart had been injured by a recognized disease process other than the primary one. The duration of the illness, from onset of symptoms to death, is short in the majority of cases of myxoma of the left atrium—in this case, approximately one year. The course depends upon the location of the tumor, the rapidity of its growth, the degree of involvement of the myocardium, and the size and length of the pedicle. A number of features originally suggested the presence of progressive, subacute interstitial pulmonary fibrosis (Hamman-Rich syndrome) or metastatic carcinoma. The congestive heart failure was refractory to the usual therapy.

The absence of any murmurs, along with appreciable enlargement of the left atrium, suggests that the obstruction of blood flow in the left atrium occurred at the orifices of the pulmonary veins rather than at the mitral valve.⁶ Indeed,

chronic obstruction of the orifices of the pulmonary veins explains the respiratory difficulties. The association of low grade fever and anemia with myxoma of the heart is an extremely interesting one, and the possible explanation for the systemic reactions might be the presence of the tumor itself. The presence of hemorrhage or necrosis inside the myxoma may have been responsible for some of the low grade fever.

From the extensive review of cardiac tumors by Prichard,¹⁰ it appears that approximately one-half are of the type observed in our case, that is, the so-called myxoma. It has been reported in patients from the age of three months to 68 years, the majority of cases occurring between 30 and 60 years, with equal sex distribution. About 75% of these tumors occur in the left atrium. The evidence leading to the controversy among pathologists as to whether the lesion is a true neoplasm or simply an organized thrombus was weighed by Prichard,¹⁰ who said: "The myxomas are thus seen to form a uniform group of tumors, occurring in a definite location in the heart and having a characteristic gross and microscopic appearance. Aside from bearing superficial similarities to some thrombi, there is little to indicate that they are thrombi or arise from them, and the bulk of evidence indicates, that they are true neoplasms. Mechanical factors are probably responsible for the frequent myxoid character of these connective tissue tumors." Cardiac catheterization data included in a report of six patients with left atrial myxoma⁵ revealed the pulmonary capillary pressure to be elevated in five patients.

Neither conventional roentgenography nor electrocardiographic tracings have been helpful in establishing the diagnosis of atrial myxoma. However, intracavitary tumors have been diagnosed in life by means of angiocardiology (Steinberg, Dotter, and Glenn^{5, 13}). In the presence of unexplained progressive intractable congestive cardiac failure, angiocardiology has proved to be a definitive method for diagnosis of intracavitary tumor. Characteristic persistent filling defects in an enlarged atrium were noted in all cases.

It is of interest that at one time the decision was made to operate for the purpose of establishing a definite diagnosis. However, upon administration of the anesthetic the patient went into shock. In retrospect, this might have suggested intracardiac tumor. Recent advances in surgical technics have made it possible to remove intracavitary tumors successfully. The following communication was received from Scannell:¹¹

The patient whom I reported at the New England Cardiovascular Society, November 14, 1955, was a 32-year-old man who had the classic history of mitral stenosis and whom we operated upon with that diagnosis. At the time of operation we discovered a large intra-atrial tumor, but postponed trying to remove it at that time until we could do so under hypothermia. His second operation was on June 15th of this year. We had the patient cooled to 26° C.—we were then able to interrupt his circulation for the five or six minutes necessary to open his atrium and remove the tumor. The operation was complicated by ventricular fibrillation which fortunately reverted to normal rhythm after two hours of massage and electric shock. The patient following this had a good recovery and now, six months later, has returned to work in good health.

At the time we did this operation we were unaware that two successful cases had been reported previously—one by Clarence Crafoord which was reported in *Circulation* in June of this year and was also reported at the International Symposium

held at the Henry Ford Hospital this spring and published by W. B. Saunders. A second case was done in May of this year by William Bigelow in Toronto and this he reported at an International Symposium in Stockholm. The Crafoord case was done with a heart lung machine and the Bigelow case was done with hypothermia. We plan to submit the details of our patient in the *New England Journal of Medicine*¹² in the very near future.

SUMMARY

A case is reported of genuine myxoma of the left atrium in which the diagnosis was established at postmortem examination.

The absence of any type of murmur and the presence of low grade fever and anemia had led to innumerable unsuccessful clinical investigations. The symptoms and signs are thought to have resulted from mechanical interference with entrance of blood into the left heart and to back pressure in lungs and right heart.

The chest films were compatible with severe, progressive pulmonary congestion, and electrocardiographic tracings reflected a right heart strain pattern. It is suggested that with these findings, coupled with persistent, progressive cardiac insufficiency, entirely unresponsive to treatment, intracardiac tumor should have been suspected.

Angiocardiography is a specific aid to diagnosis in such cases and is urgently advised, since this type of tumor now can be successfully removed and represents one form of curable heart disease.

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SUMMARIO IN INTERLINGUA

Myxoma del corde ha essite diagnosticate ante morte solmente in rar casos. Le disordine es usualmente misprendite pro stenosis mitral.

Le patiente del presente reporto, un menagera de 54 annos de etate, habeva un historia de plure previe morbos. Le autor suspice que istos habeva coexistite con le maladia que resultava in su morte. Super le base de observationes clinic, roentgenologic, e electrocardiographic un diagnose de extension lymphatic de un carcinoma metastatic a transverso ambe pulmones, originari ab adenocarcinoma del mamma dextere, esseva prendite in consideration. Altere diagnoses regardate como possibile esseva morbo collagenic e progressive subacute fibrosis pulmonic interstitial. Nulle murmures cardiac esseva audibile, mesmo in position recumbente sinistro-lateral. Basse grados de febre e anemia remaneva sin explication. Le disfallimento congestive se monstrava refractori al usual therapia.

Al autopsya le corde pesava 323,5 g. Le atrio sinistre contineva un lobulate grisastre massa tumoral que mesurava 5,5 cm in longor, 4 cm in largor, e 1,2 cm al base. Le base del tumor esseva attachate al margine superior del foramine oval. Sectiones del tumor revelava forte fibrosis, con formation de cartilagine e mesmo un certe grado de calcification. In iste areas il habeva etiam alicun signos de ancian hemorrhagia. Al peripheria, le tumor formava un rete pauc dense de elongate cellulas fusiforme. In le spatios inter iste cellulas, un matrice esseva notate consistente de un homogenee materia metachromatic que suggereva le presentia de grande quantitates de mucina. Le controversia inter pathologos in re le question si le

myxoma es un ver neoplasma o simplemente un thrombo organisate esseva ponderate. Le autor crede que iste tumor se originava ab un sito definite del endocardio e haveva le characteristic apparentia macro- e microscopic de un ver neoplasma.

Le absentia de murmures cardiac indicava que le obstruction del fluxu sanguinee in le atrio sinistre occurreva al orificio del venas pulmonar plus tosto que al valvula mitral. Le association de basse grados de febre e de anemia con myxoma cardiac es interessantissime. Le explication del reaction systemic es possiblementemente a trovar in le presentia del tumor mesme. Ni roentgenogrammas conventional ni registrationes electrocardiographic se ha provate de valor in establir le diagnose de myxoma atrial. Datos de catheterisation cardiac ha essite reportate que revelava un elevation del pression pulmo-capillar. Tamen, tumores intracavitari ha essite diagnosticate in vivo per medio de angiocardigraphia. Characteristic defectos persistente del repletion atrial esseva notate in omne casos. Recente progressos del technica chirurgic insimul con le uso de hypothermia o un machina cardio-pulmonic ha rendite possibile le ablation de tumores intracavitari con bon successo.

In le caso del presente reporto, le symptommas e le signos esseva interpretate como resultados de un obstruction mechanic del entrada de sanguine in le corde sinistre e de un pression retrorse in le pulmones e le corde sinistre. Iste observationes esseva associate con persistente progressive insufficientia cardiac que remaneva totalmente refractori al tractamento. Tumor intracardiac deberea haber essite suspicite.

Le revista del litteratura indica que angiocardigraphia es un specific adjuta diagnostic in casos de iste genere. Su uso es urgentemente recommendate, proque le typo de tumor sub consideration pote hodie esser abferite con bon successo. Illo representa un forma curabile de morbo cardiac.

BIBLIOGRAPHY

1. Block, W. J., Parker, R. L., and Edwards, J. E.: Cardiac clinics: "Myxoma" of the left atrium clinically simulating mitral stenosis: report of case and pathologic studies, *Proc. Staff Meet., Mayo Clin.* 27: 361-371 (Sept. 10) 1952.
2. Coulter, W. W., Jr.: Myxoma of the heart (left auricle), *Arch. Path.* 43: 86-91 (May) 1950.
3. Davis, T. W., and Andrus, E. C.: Mitral stenosis in facsimile, *New England J. Med.* 251: 297-302, 1954.
4. Goldberg, H. P., Glenn, F., Dotter, C. T., and Steinberg, I.: Myxoma of the left atrium. Diagnosis made during life with operative and postmortem findings, *Circulation* 6: 762-767 (Nov.) 1952.
5. Goldberg, H. P., and Steinberg, I.: Primary tumors of the heart, *Circulation* 11: 963-970 (June) 1955.
6. Harrison, J. W., McCormack, L. J., and Ernstene, A. C.: Myxoma of the left atrium simulating mitral stenosis, *Circulation* 10: 766-771 (Nov.) 1954.
7. Likoff, W., Geckeler, G. D., and Gregory, J. E.: Functional mitral stenosis produced by an intra-atrial tumor, *Am. Heart J.* 47: 619-625 (Apr.) 1954.
8. Maronde, R. F.: Case reports of two primary cardiac neoplasms, *Am. Heart J.* 49: 124-126 (Jan.) 1955.
9. Martin, B. F.: Clinical aspects of myxoma of the left auricle, *Ann. Int. Med.* 38: 325-331 (Feb.) 1953.
10. Prichard, R. W.: Tumors of the heart. Review of the subject and report of one hundred and fifty cases, *Arch. Path.* 51: 98-128 (Jan.) 1951.
11. Scannell, J. G.: Personal communication to the author.
12. Scannell, J. G.: Successful removal of a myxoma from the left atrium, *New England J. Med.* 254: 601-604, 1956.

13. Steinberg, I., Dotter, C. T., and Glenn, F.: Myxoma of the heart, roentgen diagnosis during life in three cases, *Dis. of Chest* **24**: 509 (Nov.) 1953.
14. Weinstein, M., and Arata, J. E.: Mitral stenosis and insufficiency produced by cardiac "myxoma," *Am. Heart J.* **38**: 781-787 (Nov.) 1949.
15. Young, R. D., and Hunter, W. C.: Primary myxoma of the left ventricle with embolic occlusion of the abdominal aorta and renal arteries, *Arch. Path.* **43**: 86-91 (Jan.) 1947.

TRICUSPID OCCLUSION DUE TO MASS THROMBUS OF THE RIGHT AURICLE *

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ANTEMORTEM formation of mural thrombi within the various chambers of the heart is a not uncommon occurrence. Garvin,¹ of the Cleveland City Hospital, in 1941 reported 265 instances in 6,285 consecutive postmortem examinations. The largest percentage of these was found in patients with coronary artery disease with infarction. The next largest groups were hypertensive and rheumatic heart disease. Usually these thrombi are important only as sources of peripheral emboli. However, occasionally these may be of such magnitude that the general circulation is embarrassed.

In 1814 William Wood² detected at necropsy a large ball valve thrombus in the left auricle which had obstructed the flow of blood, he believed, through a stenotic mitral orifice. Von Ziemssen³ in 1890 felt that no clear distinction should be made between large free thrombi and pedunculated auricular thrombi, since both could produce the same symptoms.

Evans and Benson⁴ (1948) have used the term "mass thrombus" to describe a clot that forms in the left auricle during life and, by reason of its large size or its peculiar location, impedes the flow of blood through the mitral orifice. This term includes attached, pedunculated and ball thrombi, avoids ambiguity in the definition of "ball thrombus," and specifies obstruction of blood flow through the mitral valve as the important factor in its definition.

Von Ziemssen postulated that mitral stenosis is necessary for thrombus formation. Garvin⁵ believed that auricular fibrillation is an additional important factor because it causes incomplete emptying of the heart, which in turn favors formation and possible detachment of mural thrombi. Mitral stenosis was shown not to be an essential factor when a case of pedunculated thrombus in the left auricle was reported in 1931⁶ in a hypertensive heart and again in 1935,⁷ and a third case was reported by Strade in 1950.⁸

There are 15 earlier references in the literature of occlusion of the tricuspid valve by a thrombus. In five of these, damage to the tricuspid valve was present, four due to rheumatic fever and one to acute bacterial endocarditis due to Fried-

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länder's bacillus. There were also four cases with a history suggestive of rheumatic fever, but the autopsy findings in this respect were either not conclusive or were not definitely stated. In six cases the heart was apparently normal. Two of these were associated with pulmonary tuberculosis, one followed splenectomy, and one case was a three week old infant. In only one case, that of Wright, Flynn and Druet in 1944,⁹ was the correct diagnosis made ante mortem. Many of these cases have shown a very similar clinical course of severe intermittent dyspnea, cyanosis, and rapid temporary recovery.

Probably the first reported incident of occlusion of the tricuspid valve was that of Zorzati¹¹ in 1832. He reported a case of a 22 year old male presenting symptoms referable to the gastrointestinal tract and palpitations for three years. He showed progressive heart failure during this period, with fever and night sweats. Fibrillation probably was present. At autopsy the heart was four times the normal size, with dilatation primarily of the right auricle, in which was found a large pedunculated tumor weighing four ounces. It was adherent to the auricle and plunged into the right ventricle. No histologic examination was made, but the four doctors present were of the unanimous opinion that it represented a thrombus.

The second case is that of Proust¹² in 1864. He reported a case of a 58 year old male who, following severe trauma to the chest, began to have pulmonary symptoms and developed a systolic murmur suggestive of mitral disease. He showed progressive dyspnea, palpitation and cyanosis. The diagnosis was felt to be a pulmonary infarction; however, the autopsy was limited to the heart and was therefore inconclusive. A pedunculated tumor of the right auricle was found; it was pear-shaped, 7 cm. in length, and extended through the tricuspid valve. The histologic summary was inconclusive, but it was probably an organized thrombus.

The third case and the first clinical report in the English literature was that of McLeod in the *Edinburgh Medical Journal* in 1882. The course in this case was quite similar to that of many of the later cases, and the conclusions drawn by McLeod appear to be valid. Briefly, his case was as follows: A man, 27 years of age, with no apparent underlying cardiac pathology, while recovering from a thigh wound was suddenly seized with "rice-water" diarrhea and vomiting, which persisted for two days and then was followed by an itching skin eruption. The patient seemed to convalesce, but on the fifth day he was seized with a convulsion and immediately lapsed into unconsciousness, dyspnea and cyanosis. A diagnosis of probable pulmonary embolism was made. Diarrhea was persistent and involuntary. The convulsive attack repeated itself in the evening and he never recovered consciousness. He had quiet delirium on the sixth day and died on the seventh day.

On postmortem examination several soft, small, yellow antemortem clots were found in the left side of the heart. The right auricle contained a very firm, almost cartilaginous, grayish yellow, movable clot, half as large again as a walnut, lying over the tricuspid orifice.

McLeod expressed his belief that the first convulsive attack was brought on by a partial occlusion of the tricuspid valve by this clot; with the weakening of the heart action the clot fell away, thus accounting for the period of improvement between the first and second attacks. He suggested that, had he known the real

condition, he would have tilted the bed in an effort to displace the clot. This case has not been accepted by the majority of authors as a true case of ball valve thrombosis. However, it meets the criteria of the mass thrombus as set forth by Evans and Benson in 1948. The thrombus was sufficient to occlude the tricuspid orifice.

In 1893, Krumbholz¹³ reported a fourth case, that of a 58 year old male. The clinical diagnosis was chronic peritonitis; however, the history was more suggestive of cirrhosis. On physical examination no heart disease was evident. Autopsy revealed an organized thrombus of the right auricle with a pedicle attached to the lateral wall, the bulk of the thrombus obliterating the cavity of the right auricle. The thrombus was found to be larger in diameter than the tricuspid valve and propagated into the venae cavae. Microscopic examination showed this to be an organized thrombus. In the same year, Kullmann¹⁴ reported the fifth case, that of an infant female whose birth was without complications and who had been in good health until three weeks of age. At that time the mother found the child to be cyanotic. The child did not recover from this and died three days later. At autopsy a large tumor was found which filled the right auricle and obstructed the tricuspid valve. It was attached to the wall of the auricle and had propagated itself into the venae cavae and extended through the tricuspid valve. Microscopic examination revealed an organized thrombus having its origin in a subendocardial hemorrhage.

In 1901 Simmonds¹⁵ reported the sixth case, a mass thrombus of the right auricle as an incidental finding at autopsy of a 24 year old male who had died of pulmonary tuberculosis and tuberculosis involving the adrenal gland. The only cardiac symptom that could be elicited was precordial pain for four months. There was no dilatation of the heart, and no murmurs were heard. At autopsy, when the right auricle was opened, a multitude of nodules was found to fill the chamber, with three of the larger nodules approximately the size of a hazel nut. These were lobulated and pedunculated, with a smooth, shiny surface. Microscopic examination revealed an organized thrombus covered with endothelium. Weltmann¹⁶ in 1920 reported a seventh case, occlusion of the tricuspid valve in a 20 year old male dying of pulmonary tuberculosis who had shown progressive dyspnea for two months and enlargement of the abdomen. At first tachycardia was present, but it responded to digitalization. During this period the heart was observed to dilate progressively. At autopsy a tumor the size of a fist was found in the right auricle on a pedicle arising 3 cm. above the tricuspid valve. The tumor was found to be engaged in the valvular orifice. Microscopic examination showed an organized thrombus. The eighth case was reported by Husten¹⁷ in 1923. This patient was a 24 year old male who had had a splenectomy for hemolytic jaundice. During the postoperative period he died suddenly, suggesting a pulmonary embolus. At autopsy a pulmonary embolus was found which probably arose from the femoral vein. However, the right auricle contained a large tumor the size of an apple, smooth, 8.5 cm. by 6.5 cm., attached between the venae cavae. It was found to be engaged into the tricuspid valve and entered the right ventricle for a distance of 2.5 cm. The valve cusps were healthy. Microscopic examination revealed an organized thrombus showing all stages of organization.

The case reported by Wright, Flynn and Druet (1944) has been the only case diagnosed correctly ante mortem. They based their conclusion on the

following points: (1) cyanosis of face and neck; (2) engorgement of veins; (3) marked dyspnea of the air-hunger type; (4) marked enlargement of the right side of the heart, especially the right auricle; (5) the presence of old rheumatic heart disease (almost universal); (6) auricular fibrillation; (7) mitral stenosis (not believed essential); (8) the presence of a murmur which could be established definitely as one of tricuspid insufficiency or stenosis; (9) engorgement of liver; (10) a series of striking variations of the syndrome, from extreme severity to relatively normal conditions and vice versa within short periods of time (six to 48 hours). Particularly noted were the marked changes in the roentgenogram of the heart within 48 hours. Autopsy in this case revealed old rheumatic heart disease with severe mitral stenosis, with mural thrombi in the left auricular appendage and multiple peripheral secondary infarcts, and a ball thrombus (diameter, 6.8 cm.) in the right auricle.

Calvino¹⁸ in 1948 reported two cases of thrombi occluding the tricuspid valve. He does not state the underlying pathology that was present; however, the illustrations accompanying the case reports are suggestive of rheumatic valvulitis involving the tricuspid valve. In 1951 Radding¹⁹ reported a case of ball thrombus of the right auricle associated with acute bacterial endocarditis due to Friedländer's bacillus. Moia and Hojman²⁰ in 1951 reported a case of free thrombus in the tricuspid auricle orifice, partly in the right auricle and partly in the ventricle. This patient had old rheumatic heart disease involving the mitral and aortic valves, but no evidence was present of involvement of the tricuspid valve. In 1955 Lui and Musselman²¹ reported a case of large ball thrombus of the right auricle in a 57 year old man with a history of rheumatic fever. However, at autopsy no evidence of mitral stenosis was present, and the possibility of rheumatic heart disease was apparently not conclusively determined. In 1956 Frommer²² reported a case of a 69 year old white woman with a ball thrombus in the right auricle, and calcification and stenosis of aortic valve and chronic rheumatic endocarditis.

CASE REPORT

A 64 year old female, a known hypertensive for 10 years, had remained fairly well compensated until five years prior to death, at which time she had an episode of dyspnea and cyanosis, and rhonchi were heard throughout both lung fields. She responded to the usual cardiac régime and was able to do light housework following this for a period of one year. She then had a similar episode of pulmonary edema, was hospitalized, and gradually improved. After this it was impossible for her to do her own housework. She remained fairly well compensated on a very strict régime until three days prior to death, at which time she became dyspneic and cyanotic, and was hospitalized. She responded to the usual emergency measures and was doing quite well when suddenly, on the third hospital day, after eating her lunch, she fell over and died after gasping for breath several times.

Autopsy revealed a heart weight of 800 gm. The left ventricular wall measured 28 mm.; the right, 8 mm. When the right auricle was opened a firm, attached clot floated out. This thrombus measured 7 cm. in length and 2 cm. in diameter, and extended down through the tricuspid leaflets into the right ventricle for a distance of 2.5 cm. (figure 1). Both coronary arteries showed marked sclerotic changes, but the lumen remained patent throughout. The mitral valve was normal and there were no mural thrombi in the left auricle.

The left lung weighed 350 gm.; the right, 430 gm. On the anterior surface of

both lungs, there were numerous petechial hemorrhages measuring 0.1 to 0.3 cm. in diameter. These were pink in color and subpleural in character, and did not extend into the substance of the lung.

Microscopic examination of the thrombus showed a typical antemortem lamination. Examination of the attachment of the thrombus to the myocardium showed the network of fibrin with enmeshed leukocytes and erythrocytes extending between



FIG. 1. Thrombus, 7 cm. in length and 2 cm. in diameter, attached firmly to the wall of the right auricle and extending downward through the tricuspid leaflets.

the muscle bundles. This had the appearance of a fairly recent process. The left lung showed marked atelectasis of the lower lobe and an increased interstitial tissue, and one section showed slight overdistention of the alveoli taken from the apex.

DISCUSSION

The clinical picture of ball valve thrombi of the left side of the heart has been well described. However, the extreme rarity of this phenomenon on the

right side of the heart has made antemortem diagnosis most difficult. Mahaim,²³ in his extensive review of the subject, concludes that we have little that is consistently present to make a syndrome of right auricular polyp. If the mass produces an insufficiency of the tricuspid valve, a venous pulsation may be observed. The tricuspid lesion will be camouflaged by the associated mitral lesion which is so frequently present. In like manner, the pulmonary symptoms due primarily to the mass may be confused with those of a pulmonary infarction which may or may not be associated. Paroxysms of auricular fibrillation without apparent cause have been observed in cases of a mass in the right auricle. He concludes that, at present, observation radiographically of progressive dilatation of the right auricle, especially if associated with signs of obliteration of the vena cava, is the most helpful diagnostic sign.

SUMMARY

The first case of tricuspid occlusion due to mass thrombus of the right auricle associated with hypertensive heart disease is presented. A review of the previous cases of occlusion of the tricuspid valve is given.

SUMMARIO IN INTERLINGUA

Es presentate le caso de un femina blanc de 64 annos de etate, cognoscitamente hypertensive, qui moriva subitemente e in qui le necropsia revelava un thrombo massa occludente le valvula tricuspid.

Le formation ante morte de thrombos mural intra le varie cameras del corde non es un occurrentia incommun. Le plus grande procentage de istos ha essite trovate in patientes con morbo del arteria coronari e infarcimento. Le secunde gruppo importante esseva casos de hypertension e morbo cardiac rheumatic. Tal thrombos es generalmente significative solmente como fontes de embolos peripheric. In 1814 William Wood detegeva un grande thrombo valvular globular in le auriculo sinistre. Iste thrombo, secundo Wood, habeva obstruite le fluxo de sanguine in consequentia de un stenotic orificio mitral. In 1880 von Ziemssen opinava que un distinction nette non deberea esser facite inter grande thrombos libere e pedunculate thrombos auricular, proque ambe typos produceva le mesme symptomatas.

In 1948 Evans e Benson usava le termino "thrombo massa" pro describer un coagulo que se forma in le auriculo sinistre durante le vita del patiente e que—a causa de su grande dimensiones o de su location particular—impedi le fluxo de sanguine a transverso le orificio mitral. Iste termino include thrombos attachate, pedunculate, e globular. Le factor importante in su definition es—secundo Evans e Benson—que le thrombo massa obstrue le fluxo de sanguine a transverso le valvula mitral.

Originalmente on credeva que stenosis mitral esseva necessari pro le formation de thrombos obstructive. Tamen, tres casos de "thrombos massa" es describe in le litteratura como occurrente in morbo cardiac hypertensive.

Le litteratura cognosce 13 previe casos de occlusion del valvula tricuspid per un thrombo. In cinque de iste casos le valvula tricuspid esseva ledite: in quatro per febre rheumatic e in un per acute endocarditis bacterial causate per le bacillo de Friedländer. In tres casos additional un historia es presentate que suggere febre rheumatic, sed le constatationes necroptic non esseva conclusive o non esseva formulate definitemente. In cinque casos le corde esseva apparentemente normal. Duo de illos esseva associate con tuberculose pulmonar; le tertie esseva post-splenectomic; e in le quarte il se tractava de un infante de tres septimanas de etate. Le correcte diagnose esseva establite ante morte in solmente un caso, illo de Wright, Flynn, e

Druet in 1944. Le caso del presente reporto es le prime que concerne occlusion del valvula tricuspid in association con morbo de hypertension cardiovascular.

Le patiente habeva essite hypertensive durante dece annos. Su ultime maladia cominciava tres dies ante su morte. Illa deveniva dyspneic e cyanotic e esseva hospitalisate. Illa respondeva al usual mesuras de urgentia, sed le tertie die de su sojorno al hospital illa moriva subitemente.

Le necropsia revelava un peso del corde de 800 g. Le pariete sinistro-ventricular mesurava 28 mm, le pariete dextero-ventricular 8 mm. Quando le auriculo dextere esseva aperite, un thrombo solide esseva trovate attachate al pariete del auriculo dextere e positionate supra le valvula tricuspid. Le thrombo esseva 7 cm longe e habeva un diametro de 2 cm. Illo se extendeva a in le ventriculo dextere a un distantia de 2,5 cm. Le examine microscopic monstrava le typic apparentia de un thrombo de formation ante morte.

BIBLIOGRAPHY

1. Garvin, C. F.: Mural thrombi in the heart, *Am. Heart J.* **21**: 7-13, 1941.
2. Wood, W.: Letter enclosing the history and dissection of a case in which a foreign body was found within the heart, *Edinburgh Med. and Surg. J.* **10**: 50, 1814.
3. Von Ziemssen: Zur Pathologie und Diagnose der gestielten und Kugelthromben des Herzens, *Congress f. inn. Med.* **9**: 281, 1890.
4. Evans, W., and Benson, R.: Mass thrombus of the left auricle, *British Heart J.* **10**: 39, 1948.
5. Garvin, C. F.: Ball thrombi in the heart: report of 3 cases, *Am. Heart J.* **21**: 371, 1941.
6. Schwartz, S. P., and Biloon, S.: The clinical signs of occluding thrombi of the left auricle, *Am. Heart J.* **7**: 84, 1931.
7. Kaplan, D., and Hollingsworth, E. W.: Pedunculated thrombus of the left auricle simulating mitral stenosis, *J. A. M. A.* **105**: 1264, 1935.
8. Strade, H. A.: Pedunculated ball thrombus in a hypertensive heart, *J. A. M. A.* **143**: 1409, 1950.
9. Wright, I. S., Flynn, J. E., and Druet, K. L.: Ball thrombus in the right auricle of the heart, with description of symptoms produced, *Am. Heart J.* **27**: 858-869, 1944.
10. Mcleod, N.: A movable clot in the right auricle, *Edinburgh M. J.* **28**: 696, 1882-3.
11. Zorzati, E.: Corpo straniero nell'orecchietta e ventricolo destro del cuore, con ingrandimento dei questo e del fegato, *Annali Universali di Medicina* **41**: 268, 1832.
12. Proust: Observation d'un polype due l'oreillete droite, *Compt. rend. Soc. de biol.* **16**: 51, 1864.
13. Krumbholz, H.: Zur Casuistik der gestielten Herzpolypen und der Kugelthromben, *Arb. a. d. med. Klin. z. Leipzig* **328**, 1893.
14. Kullmann, H.: Zur Casuistik alterer Thrombenbildungen in den Hohlvenen und den Vorhofen, *These de Giesen*, 1893.
15. Simmonds: Primäre Herzgeschwülste, *München. med. Wchnschr.* **48**: 649, 1901.
16. Weltmann, O.: Klinischer Beitrag zur Kasuistik primärer Herztumoren, *Wien. klin. Wchnschr.* **33**: 537, 1920.
17. Husten, K.: Über Tumoren und Pseudotumoren des Endokards, *Beitr. z. path. Anat. u. Physiol.* **71**: 132, 1923.
18. Calvino, J.: Thrombosis obliterante de la auricula derecha, *Rev. cubana de cardiología* **9**: 1, 1948.
19. Radding, R. S.: Ball thrombus of the right auricle, *Am. Heart J.* **11**: 653, 1951.
20. Moia, B., Manguel, M., and Hojman, D.: Trombo en bola de la auricula derecha, *Rev. argent. de cardiología* **18**: 320, 1951.
21. Lui, A. H. F., and Musselman, M. M.: Intracavitary cardiac masses: diagnosis and treatment, *Am. Heart J.* **50**: 934, 1955.
22. Frommer, F.: Ball-thrombus of the right atrium, *Brit. Heart J.* **18**: 137, 1956.
23. Mahaim, I.: Les tumeurs et les polypes du coeur, 1945, Masson & Cie., Paris.

EMERGENCY TREATMENT OF BARBITURATE INTOXICATION WITH HEMODIALYSIS*

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BARBITURATE intoxication is an important cause of morbidity and mortality. The following case report describes a severe case of barbiturate intoxication in which hemodialysis, as recently recommended by Kyle² and Alwall,¹ was applied. Since we have noted reports of only five patients with barbiturate intoxication¹⁻⁴ treated by hemodialysis, the striking clinical changes in a patient during hemodialysis prompted a report of this case.

CASE REPORT

A 63 year old white married woman was admitted to the Albany Hospital Emergency Room in coma at 5:00 p.m. Her husband related that the patient had been moody and depressed for the previous four weeks. At 1:00 p.m. on the day of admission he found the patient staggering about the house. Three hours later he found her lying unresponsive beside an empty bottle of meperidine hydrochloride and an empty bottle of Tuinal (equal parts of amobarbital and secobarbital).

Physical examination on admission revealed a comatose woman who was without visible spontaneous respirations. Blood pressure was 60/0 mm. of Hg; pulse, 46. The airway was open. Neither deep nor superficial reflexes were present. The eyes were open and staring with dilated pupils which reacted to light. The patient did not respond to any stimuli. The heart tones were muffled and soon disappeared entirely. The extremities were cyanotic and cold. The remainder of the physical examination was negative.

Respiration was initiated and maintained by an intermittent positive pressure apparatus. Five milligrams of nalorphine hydrochloride at 5:30 p.m. and at 6:00 p.m. were without effect. Vascular collapse was treated with intravenous phenylephrine hydrochloride. A blood sample drawn at 6:00 p.m. showed a barbiturate level of 5.25 mg.%.³†

At 11:00 p.m., approximately six hours after admission, therapy was started with a Kolff modified artificial kidney. At this time the unimpeded radial artery flow was 50 c.c. per minute, although the blood pressure supported by phenylephrine was 108/25 mm. of Hg. After 45 minutes of dialysis the patient demonstrated bilateral clonus of the legs when the plantar reflex was elicited.

At this time the patient began to breathe spontaneously with her diaphragm. After 70 minutes of dialysis she had acquired a spontaneous respiratory rate of 20 per minute. Both the ankle and the knee jerks returned.

After 90 minutes thoracic breathing was noted. The radial artery flow was 108 c.c. per minute. After 180 minutes the heart tones became audible for the first time in eight hours. After 240 minutes of dialysis the patient was moving spontaneously.

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† We are indebted to the New York State Police Laboratory for the determinations of barbiturate levels included in this report. The method of Goldbaum⁵ was used. A Tuinal standard was used, and the exact amounts of amobarbital and secobarbital were not determined.

The dialysis was terminated after 330 minutes. The blood concentration of barbiturate at this point was 2.0 mg. %.

At 8:00 o'clock the next morning, approximately 19 hours after ingesting the drug, the patient was awake, oriented and quite alert. She was able to eat a regular diet for breakfast. She was transferred to the Psychiatric Service and after five days was discharged to her home.

DISCUSSION

Questioning revealed that this patient had ingested from 2 to 2.5 gm. of a moderately fast-acting combination of amobarbital and secobarbital. According to Fisher and Freimuth,⁶ the moderately acting barbiturates cause coma with a blood level of 1 to 2 mg. %. This case was further complicated by the ingestion of meperidine, which might augment the depressive activity of the barbiturate.

There are, in general, three therapeutic approaches to barbiturate intoxication: first, supportive therapy, comprising maintenance of the airway, parenteral alimentation, and antibiotics; second, analeptics; and third, efforts to increase excretion of barbiturates. Supportive therapy is quite satisfactory for patients with good reflexes in the first three categories of Sunshine and Hackett⁷ and Reed et al.⁸ Analeptics such as picrotoxin, Metrazol or nikethamide are usually used in treating patients who are comatose and without reflexes (fourth category), or in respiratory and vascular collapse (fifth category) as well. Mortality in the fourth category is about 20% and in the fifth category 35%.⁸ Efforts to increase excretion of barbiturates have also been used to help patients in the fourth and fifth categories, and have consisted of forced polyuria, exchange ultrafiltration and hemodialysis.

Studies by Alwall, Sunshine and Leonards, and Kyle et al., have shown that hemodialysis is an efficient means of increasing barbiturate excretion. Alwall¹ found that hemodialysis lowered blood concentrations of phenobarbital in dogs over four times as rapidly as normal renal excretion and more than twice as rapidly as excretion increased by forced polyuria. Sunshine and Leonards⁹ showed in dogs that hemodialysis cleared phenobarbital about 10 times as fast as the kidneys, amobarbital six to seven times as fast, and pentobarbital about 16 times as fast. Observations on patients reported by Kyle et al.² indicated that hemodialysis removed phenobarbital from the body about 16 times as rapidly as the kidneys, and Amytal about 30 times as rapidly.

Slightly over 1 gm. (1.050 gm.) of barbiturate was removed by hemodialysis in this case, and striking clinical improvement occurred during dialysis. A review of 36 cases of barbiturate intoxication disclosed nine clinically comparable cases, with barbiturate ingestion of 2.0 ± 0.3 gm.^{8, 10} These cases were treated by supportive measures and analeptics. The average duration of coma was 47 hours, but one case with coma of only 20 hours' duration and one of only 10 hours' duration were recorded. Since our patient was comatose for 19 hours, we cannot conclude that dialysis significantly shortened the period of coma.

On the other hand, the striking improvement of our patient during dialysis, in spite of augmentation of the barbiturate poisoning by the Demerol ingested and the collapse of cardiovascular and renal function, has caused us to feel that dialysis contributed greatly to this patient's recovery. At the start of the dialysis our patient had no spontaneous respiration, and her cardiovascular state

was characterized by absence of heart sounds and a blood pressure maintained with difficulty by vasopressor drugs. It is safe to say that the excretion of barbiturate from the body would be impaired under such circumstances and prolonged coma, at best, might be expected. Restoration of respiration, heart sounds and blood pressure, reflexes and spontaneous movements in four hours of dialysis is impressive.

The increase in blood flow from the radial artery is worthy of further note. A relatively low outflow of blood from a cannulated radial artery into the artificial kidney is seen in patients with markedly reduced cardiac output. The rate of initial unimpeded flow from the radial artery cannula of 50 cubic centimeters per minute is so markedly low as almost to preclude hemodialysis. The increase in flow as dialysis went on to a rate later on of over 200 cubic centimeters per minute is quite certainly a direct consequence of the improvement in cardiac output and vascular tone during dialysis. This rapid improvement in the state of circulation is an important reason for the use of hemodialysis in patients critically depressed by barbiturates.

CONCLUSION

Acute barbiturate poisoning may represent a medical emergency, since severe poisoning may result in death from a potentially correctable insult. The artificial kidney is an efficient agent in promoting the excretion of barbiturates. The marked improvement of this patient during four hours of artificial kidney treatment suggests that in some instances hemodialysis may be life-saving.

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SUMMARY IN INTERLINGUA

Un frappante melioration clinic durante tractamento per hemodialyse esseva observate in un femina de 63 annos de etate con sever intoxication a barbiturato. Le patiente esseva admittite al hospital a 17 horas. Illa esseva comatose. Quatro horas prevemente su marito habeva notate que illa titubava. Un hora prevemente ille habeva trovate la jacente in stato non-responsive juxta un vacue bottilia de hydrochloruro de meperidina e un vacue bottilia de Tuinal (proportiones equal de amobarbital e secobarbital). Le historia subsequente revelava que le patiente habeva ingerite inter 2 e 2,5 g de Tuinal.

Al tempore del hospitalisation le patiente, in stato comatose, esseva sin respiration spontanee. Le pression sanguinee esseva 60/0 mm de Hg, e le pulso esseva 46. Le vias aeree esseva aperte. Nulle reflexo—o profunde o superficial—esseva presente. Le oculos esseva aperte e fixe. Le pupillas esseva dilatate e reageva a stimulos lumineose. Alteremente le patiente non reageva a ulla stimulo. Le tonos cardiac esseva amortite e tosto dispareva integremente. Le extremitates esseva frigide e cyanotic. Un pauco plus tarde nulle pression sanguinee esseva mesurable. Le concentration de barbiturato esseva 5,25 mg pro cento.

Le respiration esseva mantenite per medio de un apparatus a pression positive intermittente. Collapso cardiac esseva tractate con hydrochloruro phenylephrinic intravenose. Sex horas post admission al hospital, tractamento esseva initiate con le ren artificial typo Kolff modificate. A iste tempore le non-impedite fluxo del

arteria radial eseva solamente 50 cm³ pro minuta, ben que le pression sanguinee—supportate per phenylephrina—eseva 108/25 mm de Hg. Post 45 minutas de dialyse, le patiente monstrava bilateral clono del gamba sub stimulation del reflexo plantar e comenciava respirar spontaneamente con su diaphragma. Post 70 minutas de dialyse, le rapiditate spontanee del respiration eseva 20. Le reflexos tendinose al cavilia e al genu habeva retornate. Post 90 minutas, respiration thoracic habeva recomenciate, e le fluxo ab le arteria radial eseva 108 cm³ pro minuta. Post 180 minutas, sonos cardiac eseva audite le prime vice in octo horas, e movimento spontanee retornava post 240 minutas. Le concentration sanguinee de barbiturato eseva 2,0 mg pro cento. Quando le dialyse eseva arrestate post 330 minutas, 1,050 g de barbiturato habeva essite abferite.

Le matino sequente, circa 19 horas post le ingestion del droga, le patiente eseva essentialmente normal.

Le mortalitate general in intoxication a barbiturato de iste grado de severitate es 35 pro cento. In nove casos comparabile, le duration medie del coma eseva 47 horas, sed il es a notar que iste serie includeva un periodo comatose de solamente nove horas e un altere de 20 horas.

Nos opina que le rapide abferimento de barbiturato ab le corpore per medio del ren artificial—primo demonstrate per Alwall,¹ Sunshine e Leonards,⁹ e Kyle *et al.*²—eseva associate con le frappante melioration clinic e contribuiva grandemente al recuperation de iste patiente. Le melioration del stato cardiovascular del patiente—con augmento del fluxo ab le arteria radial a in le ren artificial, restauration del pression sanguinee, e retorno del sonos cardiac—es remarcabile.

BIBLIOGRAPHY

1. Alwall, N., Lindgren, P., and Lunderquist, A.: On the artificial kidney. XX. Treatment of severe phenobarbital poisoning in rabbits by means of forced polyuria, exchange ultrafiltration and dialysis, and a preliminary report on dialytic treatment of barbiturate poisoning in patients, *Acta med. Scandinav.* **143**: 288, 1952.
2. Kyle, L. H., Jeghers, H., Walsh, W. P., Doolan, P. D., Wishinsky, H., and Pallotta, A.: The application of hemodialysis to the treatment of barbiturate poisoning, *J. Clin. Investigation* **32**: 364, 1953.
3. Editorial: Hemodialysis in the therapy of barbiturate intoxication, *J. A. M. A.* **152**: 822 (June 27) 1953.
4. Brown, I. A., Ansell, A. S., and Schiele, B. C.: The use of hemodialysis in the treatment of barbiturate intoxication, *Minnesota Med.* **37**: 650, 1954.
5. Goldbaum, L. R.: Analytical determination of barbiturates, *Anal. Chem.* **24**: 1604, 1952.
6. Fisher, R. S., and Freimuth, H. C.: Barbiturates, *Postgrad. Med.* **17**: A28, 1955.
7. Sunshine, I., and Hackett, E. R.: Barbiturate studies. II. Correlation between clinical condition and blood barbiturate levels, *Am. J. Clin. Path.* **24**: 1133, 1954.
8. Reed, C. E., Driggs, M. F., and Foote, C. C.: Acute barbiturate intoxication: a study of 300 cases based on a physiologic system of classification of the severity of the intoxication, *Ann. Int. Med.* **37**: 290, 1952.
9. Sunshine, I., and Leonards, J. R.: Use of artificial kidney for removal of barbiturates in dogs, *Proc. Soc. Exper. Biol. and Med.* **86**: 638, 1954.
10. Jones, A. W., Dooley, J., and Murphy, J. R.: Treatment of choice in barbiturate poisoning, *J. A. M. A.* **143**: 884, 1950.

AN ALARMING PRESSOR REACTION TO REGITINE*

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REGITINE is generally considered safe for intravenous administration. A recent review by high authorities reiterates that its administration is followed by "no hazardous pressor responses when the patient has essential hypertension."¹ It seems timely therefore to report an alarming reaction recently observed.

CASE REPORT

The patient was a 53 year old Negro woman whose presenting complaint was precordial pain of anginal type. Her blood pressure was found to be 290/140 mm. of Hg, without pulsus alternans. Eyegrounds showed grade 2 changes. Arterial

TABLE 1

Minutes after Injection	Blood Pressure	Heart Rate
0	270/128	
$\frac{1}{2}$	264/120	
1 $\frac{1}{2}$	262/128	
2	275/136	
2 $\frac{1}{2}$	296/156	
3	296/156	
4	300+/170	132
5	300+/172	
6	300+/184	156
8	300+/184	
13	300+/160	112
17	300+/155	
20	300+/160	
23	300+/160	
27	300-296*/150	
31	284/150	
35	270/146	

* Pulsus alternans.

pulsation in the neck was marked but there was no venous distention. Premature ventricular beats were frequent, and there were systolic murmurs at the apex and at the pulmonic and aortic areas. There was no gallop rhythm. Femoral pulses were readily palpable, although popliteal, posterior tibial and dorsalis pedis pulsations were not felt. The lung bases were clear, there was no peripheral edema, and the liver and kidneys were not felt.

Chest x-ray showed marked cardiac enlargement with a dilated aorta; there was no rib-notching. The electrocardiogram showed marked left ventricular hypertrophy. Blood urea was 56 mg., but a later reading was only 37 mg. An intravenous pyelogram was normal, but the phenolsulfonphthalein test showed only 4% excretion in 15 minutes, with a total of 49% in two hours. Glitter cells were not found in several specimens of urine.

As part of a routine hypertensive study, a Regitine test was undertaken. Base line blood pressures averaged 270/128 mm. of Hg. The drug was injected intravenously (5 mg. diluted in 1 ml. water) with the patient lying flat. At the end of two

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and a half minutes the blood pressure had risen significantly, and alarming symptoms were present. Orthopnea rapidly developed, with profuse sweating, precordial pain and tachycardia. The blood pressure reached a maximum of 300 ± 184 mm. of Hg at the end of six minutes and remained at this level for several minutes. At the height of this pressor response the heart rate was 156. Twenty-seven minutes after injection, the first reading for which the systolic blood pressure had returned within range of the manometer scale, pulsus alternans was noted. By this time the alarming symptoms had substantially subsided, although the blood pressure was still $300/150$ mm. of Hg. Blood pressures taken at intervals during the test are tabulated (table 1).

The obvious possibility that some pressor substance, such as adrenalin, had been injected by mistake was immediately entertained. The test was being carried out in a clinic room which was unoccupied except for an assisting nurse, the patient and myself. Before beginning the test we had noted that the hypodermic tray contained three unbroken ampules, one each of Regitine, sterile water and adrenalin. When the reaction developed we immediately confirmed that the ampule of adrenalin remained intact upon the tray, and the sole contents of the nearby waste-can were two expended ampules, respectively labeled "Regitine" and "sterile water." There therefore seemed no reasonable doubt that Regitine was the material injected.

SUMMARY

An alarming reaction to intravenous Regitine, consisting of marked rise in blood pressure, tachycardia, pulsus alternans, profuse sweating, orthopnea and severe precordial pain, is reported.

SUMMARIO IN INTERLINGUA

Le administration intravenose de Regitina es generalmente considerate como salve. In le curso del studio rutinari de un patiente con sever hypertension essential, le injection intravenose de 5 mg de Regitina esseva sequite per un reaction alarmante, consistente de un marcate elevation del pression sanguinee ab $270/128$ a 300 ± 184 mm de Hg, tachycardia de 156, pulso alternante, transpiration profuse, e sever dolores precordial.

BIBLIOGRAPHY

1. Kvale, W. F., Roth, G. M., Wanger, W. M., and Priestley, J. T.: Pheochromocytoma, *Circulation* 14: 622, 1956.

TOXIC REACTION TO 2-METHYL-2-N-PROPYL-1,3, PROPANEDIOL DICARBAMATE (MILTOWN AND EQUANIL) *

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A NEW type of tranquilizing drug, Miltown (2-methyl-2-n-propyl-1,3, propanediol dicarbamate),¹ has been recently introduced for the treatment of anxiety, nervousness and tension states. The incidence of toxic reactions has been minimal. Selling reported adverse reactions in only three out of 187 patients treated

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with a total of 54,100 tablets. One patient had two fainting spells and a temperature of 102° F. two and one-half hours after taking two tablets. One hundred fifty milligrams of Pyribenzamine orally were given every four hours and in two days the temperature cleared and the edema subsided. Another patient developed urticaria four days after treatment with Miltown. Benadryl, 50 mg. with every dose of Miltown, controlled the urticaria. In a third patient angioneurotic edema developed after six days of Miltown therapy but cleared after one day of discontinuance of treatment.

We have observed a very severe reaction to Miltown and Equanil, with several hitherto unreported findings.

CASE REPORT

A 38 year old white male obtained Equanil from a local druggist and took a tablet at 4:30 p.m. on August 14, 1955. At 5:45 p.m. he developed a generalized rash over the body. At 7:00 p.m. he developed nausea. This was followed by chills and fever and vomiting, and he was hospitalized. The temperature was 102° F. He had a generalized erythematous rash involving the entire body up to the neck but not the face. The blood pressure was 140/80 mm. of Hg. The throat was not red, and there were no palpable nodes. The chest was clear. There was no abdominal tenderness. Intense and severe joint and muscle pains developed. He was given Demerol for pain. A blood count at 9:00 p.m. was reported as follows: white blood cells, 3,300; 59 stabs, 23 segmenters and 18 lymphocytes. Urine: specific gravity, 1.017; albumin, negative; sugar, negative; few bacteria.

The fever continued at 103° F. throughout the day. Because of the character of the rash and the prevalence of scarlet fever in the area, scarlet fever was suspected; however, it was not proved. On August 16, 1955 the hemogram revealed 13.3 gm. hemoglobin; packed cell volume, 41%; leukocytes, 22,100; polymorphonuclears, 94%; lymphocytes, 2%; eosinophils 4%. The urine and the serologic test for syphilis were negative. The patient was placed on pyribenzamine, 50 mg. every four hours; Demerol, 100 mg. as needed for pain, and 400,000 units of penicillin every 12 hours. Since the throat remained normal in appearance, the diagnosis of scarlet fever was still in doubt. The temperature dropped and the patient was discharged to his home on August 18, 1955. The rash was still present but fading. Two weeks later he desquamated.

Since there was a question of the effect of the Equanil, on October 19 the patient took one-half a tablet of Miltown and observed no effect. At 5:00 p.m. on October 20 he took an entire tablet of Miltown. At 6:15 p.m. he developed a slight rash, which became progressively worse. At 7:00 p.m. he developed a severe chill, a generalized erythematous rash, and severe generalized muscular and joint aching. The temperature was 102° F. On examination the blood pressure was 140/80 mm. of Hg; pulse, 110; respiration, 50. The throat was again negative. The lungs were clear and the heart was regular and rapid. There was marked mental confusion. There was no abdominal tenderness. The rash covered the entire body, including the face, which blanched on pressure and itched intensely. The patient was given Demerol, 100 mg., for pain relief. Because of the development of a shocklike state he was given 100 mg. Solu-Cortef, followed by 1 c.c. of ACTHAR-Gel. The temperature continued elevated, and the respirations continued short and shallow, and varied between 40 and 50 throughout the night. The following morning the temperature was 101° F. The aching was less, but the rash was still generalized and severe. He was continued on Metcorten for four days. The urine was negative. The hemogram was 13.5 gm. White blood cells, 22,500; 94% polys; 6% lymphocytes.

The fever cleared on October 23, 1955, but the rash continued until October 25, 1955. Leukocyte count on October 23 revealed a total count of 7,800, 67 polys, 2 monocytes and 31 lymphocytes.

The patient has had no further symptoms. He desquamated only under the arms at this time.

SUMMARY

An unusual reaction to 2-methyl-2-n-propyl-1,3, propanediol dicarbamate (Equanil and Miltown), consisting of chills, fever, generalized erythematous rash and marked leukocytosis with marked neutrophilia, is reported.

ADDENDUM

Since the above article was completed the following case has been observed.

A 62 year old white male was given his first tablet of Equanil by his wife at 9:00 p.m. on the night of September 4, 1956.

At 3:00 a.m. he awakened with a severe headache and a very severe chill. This lasted for 30 minutes. He developed a generalized stinging and itching erythematous rash over his entire body. The temperature remained at about 101° F. all day. He also became nauseated.

He was seen that night. On physical examination the generalized erythematous rash was found to include the palms of the hands and the soles of the feet. He had been taking Benadryl throughout the day, without improvement. He was placed on Meticorten, 5 mg. every six hours. The white count was 13,800, with 90 polymorphonuclears, 5 lymphocytes and 5 eosinophils. The temperature and rash began to subside on September 6, 1956; on September 10, 1956, he desquamated.

SUMMARIO IN INTERLINGUA

Reacciones toxic a Miltown e a Equanil ha essite extrememente rar. Es reportate un severissime reaction in un masculino blanc post un tabletta (400 mg) de Equanil. Le reaction esseva characterisate per algor, vomito, alte grados de febre, e un generalisate eczema erythematose in omne partes del corpore. Le patiente habeva intense dolores articular. Le numeration leucocytic esseva 22,100, 94 pro cento polymorphonucleares e 4 pro cento mononucleares. Le possibilitate de scarlatina esseva prendite in consideration. Le eczema esseva sequite per desquamation.

Plure septimanas plus tarde le patiente prendeva un tabletta de Miltown. Ille disveloppava un reaction similar, associate iste vice con un stato del apparentia de choc. Ille recipeva corticosteroides e drogas antihistaminic. Le numeration leucocytic esseva 22,500, 94 pro cento polymorphonucleares. Le febre durava tres dies, le eruption cinque dies. Ambe reacciones occurreva exactemente un e un quarte hora post le ingestion del droga.

Es reportate un secunde caso que exhibiva le mesme sequentia de evenimentos post le prime ingestion de un tabletta de Equanil.

BIBLIOGRAPHY

1. Selling, L. S.: Clinical study of a new tranquilizing drug, *J. A. M. A.* **157**: 1594-1596 (Apr. 30) 1955.
2. Borrus, J. C.: Study of effect of "Miltown" on psychiatric states, *J. A. M. A.* **157**: 1596-1598 (Apr. 30) 1955.
3. Lemere, F.: New tranquilizing drug, *Northwest Med.* **54**: 1098-1100 (Oct.) 1955.

EDITORIAL

THE HYPOGLUCEMIC SULFONYLUREA DRUGS—AN INTERIM EVALUATION

Because of the prominence of the hyperglucemia and the glucosuria as manifestations of diabetes mellitus, great reliance has been placed upon the correction of these abnormalities in the assessment of possible insulin substitutes. When a new agent comes to light which causes a lowering in the blood glucose concentration in normal subjects and in many diabetic patients, when this agent is effective upon oral administration and when this drug appears to be devoid of all important toxic side-reactions, it is inevitable that it be explored as a possible therapeutic agent. Such a drug, according to the clinical consensus, is 1-butyl-3-*p*-tolylsulfonylurea (Tolbutamide).

Diabetes is not, of course, synonymous with hyperglucemia and glucosuria. Rather it is a disease in which the major clearly recognized metabolic defect is an impairment, most striking in skeletal muscle, in the utilization of blood glucose. It is consequent upon this and other defects that the concentration of glucose in the blood rises and it is held by some that the hyperglucemia, far from being detrimental, is a compensatory mechanism of survival benefit to the organism, facilitating, to some degree, the carbohydrate nutrition of muscle cells.¹ Only if one subscribes to the view that the hyperglucemia is injurious *per se*,² should one anticipate benefits to the diabetic patient from a regimen which lowers the blood glucose concentration by mechanisms other than those attributed to insulin. In the argument which follows it should be borne in mind that the characteristic effect of insulin which distinguishes it from many other hypoglucemic drugs is its ability to enhance the uptake of glucose by the skeletal musculature, an effect readily demonstrable both in the intact animal and in the isolated diaphragm.

The experimental physiologist has long had at his disposal a variety of devices, such as phlorhizin poisoning or total hepatectomy, which result in a lowering in the blood glucose concentration. Not even the most enthusiastic therapist, however, would seriously advocate the application of such procedures to the diabetic patient. What, then, are the criteria by which a drug or procedure designed to replace insulin in therapy should be judged?

1. The new agent should be as free from toxicity and untoward side-reactions as insulin is. This condition appears from recent reports, to have been met, at least approximately, by Tolbutamide.

2. The new agent should, in a readily controllable fashion, be capable

¹ Soskin, S., and Levine, R.: Carbohydrate metabolism, 2nd Ed., 1952, Univ. of Chicago Press, Chicago.

² Joslyn, E. P., Root, H. F., White, P., Marble, A., and Bailey, C. C.: The treatment of diabetes mellitus, 1946, Lea & Febiger, Philadelphia, p. 349 *et seq.*

of lowering the blood glucose concentration to normal levels and of abolishing glucosuria. Here again, at least in selected cases, Tolbutamide appears to pass muster, offering the additional advantage over insulin of being effective by the oral route.

3. The new agent must correct, as insulin does, the fundamental defects in metabolism which, taken together, comprise diabetes mellitus. This criterion, thus far, Tolbutamide has not been demonstrated to meet.

The suspicion that the sulfonylurea group of drugs, of which Tolbutamide is an example, may fail to meet this last criterion stems from various sources. Perusal of the clinical literature reveals that in keto-acidosis and in surgical stress, those very situations wherein insulin is dramatically beneficial to the diabetic, the sulfonylurea drugs fail completely. It has in fact been proposed that Tolbutamide be reserved for the treatment of those diabetic patients who fail to go into ketosis when insulin is withdrawn.³ This is almost tantamount to saying that *Tolbutamide controls the symptoms of diabetes in the symptom-free diabetic patient*. Whereas certain experienced clinicians report a feeling of well-being among diabetic patients when treated with the newer oral drugs, it is difficult to determine the contribution to this feeling of escape from the daily needle and of the finding of a urine free of glucose.

Ultimately, in order to ascertain whether the new drugs meet the third criterion listed above, it will be necessary to establish in some detail the mechanism of the hypoglycemic action of these drugs. Out of the hectic researches of the past year or more a curious situation has developed in this regard. A number of plausible theories, each based upon more or less secure evidence, have been proposed to account for the hypoglycemic effect of the sulfonylurea drugs. Obstinate experimental facts have been reported, however, which appear to invalidate each theory. Space does not permit review of all the relevant evidence. Mention of the more prominent theories and of a few of the reported observations which are inconsistent with each theory may briefly be made.

Theory: The sulfonylurea drugs increase the effective peripheral concentration of insulin by antagonizing insulinase, by stimulating the β -cells of the islets of Langerhans, or by some other mechanism.

Inconsistent Findings: Were this the explanation, a similarity would be anticipated in the consequences of peripheral insulin injection and of sulfonylurea administration. However, whereas insulin injection is known to result in an increase in the arteriovenous difference in glucose concentration, in most reports (*e.g.*⁴), the administration of sulfonylurea does not do this. The sulfonylurea drugs produce a marked increase in the quantity of liver

³ Duncan, G. G.: Clinical experiences with sulfonylureas in diabetes mellitus, Preprint of Conference on Effects of Sulfonylureas and Related Compounds in Experimental and Clinical Diabetes, The New York Academy of Sciences, Feb. 14-15, 1957, pp. 15-16.

⁴ Purnell, R., Arai, Y., Pratt, E., Hlad, C., Jr., and Elrick, H.: Some observations on the mode of action of orinase, *Metabolism* 5: 778, 1956.

glycogen⁵ under conditions where insulin administration is followed by a decline in liver glycogen.

Theory: The sulfonylurea drugs increase the peripheral utilization of glucose in some fashion independent of insulin action.

Inconsistent Findings: The inconsistencies mentioned above also apply to this theory. Further, with very few exceptions, it has been reported that functional β -cells are *sine qua non* for hypoglucemic response in patients or animals treated with sulfonylurea drugs. In addition, the classical manifestations of peripheral glucose utilization, rise in the concentrations of lactic and pyruvic acids in the blood, are lacking during the hypoglucemia induced by sulfonylurea drugs.⁶

Theory: The sulfonylurea drugs, by one or another alteration of hepatic enzyme architecture, interfere with the production or the release of glucose by the liver.

Inconsistent Findings: The finding that Tolbutamide exerts its hypoglucemic effect in the totally hepatectomized animal would certainly indicate that the liver is not the sole site of action of this drug.⁷ The injection of sulfonylurea drugs into the portal vein of experimental animals produced no fall in blood glucose concentration, but, on the contrary, a hyperglucemia.⁸

Theory: The sulfonylurea drugs damage the α -cells of the islets of Langerhans or otherwise interfere with glucagon production, or they abolish the responsiveness of the liver to glucagon.

Inconsistent Findings: Several of the inconsistencies previously mentioned argue against this theory. Whereas altered responsiveness to glucagon in liver preparations exposed in vitro to sulfonylurea drugs has been reported,⁹ in the intact patient a normal glucagon response has been found despite the administration of drug.¹⁰ Histological changes in the α -cells have been described to follow the administration of sulfonylurea drugs,¹¹ but such changes have not been found by all students of the subject.¹² Since the known effects of glucagon are apparently limited to the liver, the de-

⁵ Miller, W. L., and Dulin, W. E.: Orinase, a new oral hypoglycemic compound, *Science* 123: 584, 1956.

⁶ Moorhouse, J. A., and Kark, R. M.: Physiologic actions of orinase and their relationship to the types of diabetes in man, *Metabolism* 5: 847, 1956.

⁷ Dulin, W. E., and Johnston, R. L.: Studies concerning the role of the liver in the hypoglycemic response of animals to orinase, Preprint of Conference on Effects of Sulfonylureas and Related Compounds in Experimental and Clinical Diabetes, The New York Academy of Sciences, Feb. 14-15, 1957, pp. 12-13.

⁸ Colwell, A. R., Jr., Colwell, J. A., and Colwell, A. R., Sr.: Intrapancratic perfusion of antidiabetic sulfonylureas, *Metabolism* 5: 749, 1956.

⁹ Berthet, J., Sutherland, E. W., and Marman, M. H.: Observations on the action of certain sulfonylureas, *Metabolism* 5: 768, 1956.

¹⁰ Fajans, S. S., Louis, L. H., Seltzer, H. S., Johnson, R. D., Gittler, R. D., Hennes, A. R., Wajchenberg, B. L., Ackerman, I. P., and Conn, J. W.: Metabolic effects of aryl-sulfonylurea compounds in normal men and in diabetic subjects, *Metabolism* 5: 820, 1956.

¹¹ Achelis, J. D., and Hardebeck, K.: Ueber eine neue blutzuckersenkende Substanz, *Deutsche med. Wchnschr.* 80: 1452, 1955.

¹² Creutzfeldt, W.: Pankreasbefunde bei Diabetikern nach Behandlung mit D860, *Deutsche med. Wchnschr.* 81: 841, 1956.

velopment of hypoglucemia after feeding of sulfonylurea drugs to liverless animals⁷ also militates against the present theory.

Many other theories have been entertained and many additional points of apparent inconsistency as well as many other bibliographic references might have been cited. The foregoing examples should, however, suffice to indicate the present somewhat chaotic situation. Assuming all the evidence already at hand to be correct and pertinent, it would appear that a reinterpretation of some of this evidence will be required before an internally consistent theory for the mechanism of the hypoglucemic action of the sulfonylurea drugs can be offered and accepted. A number of such reinterpretations are under consideration in various laboratories, but information is too scanty to warrant their discussion at this time.

We have then a new drug, or class of drugs, effective by mouth, which undoubtedly restores toward normal values the concentrations of glucose in blood and in urine of many diabetic patients. The mode of action, still uncertain, is apparently different in many regards from that of insulin. Until the mode of action has been clarified, it will be very difficult, in the opinion of this writer, to know with assurance whether or not we are doing the diabetic patient a favor when we lower his blood glucose concentration by the administration of a drug of the sulfonylurea group. The application of dye to the graying hair does not reverse the fundamental processes of senescence. It remains for future experiment and observation to determine whether an oral replacement for insulin has indeed been found.

DEWITT STETTEN, JR., M.D., Ph.D.

REVIEWS

Pulmonary Emphysema. Edited by ALVAN L. BARACH, M.D., and HYLAN A. BICKERMAN, M.D. 545 pages; 23.5 × 15.5 cm. The Williams & Wilkins Co., Baltimore. 1956. Price, \$10.00.

This book, edited by two outstanding students of the clinical aspects of pulmonary emphysema, actually consists of a series of essays pertaining to various aspects of the syndrome.

The first half of the book (which, in the reviewer's opinion, should be the second half) consists of a series of comprehensive and detailed discussions of the clinical management of pulmonary emphysema, as practiced by Dr. Barach and his group. There is no doubt that most of their beliefs are sound and based on long experience. However, one concept may need questioning. They strongly advocate using oxygen therapy for the hypoxic episodes in obstructive emphysema—"Among our special objectives has been an attempt to establish continuous inhalation of oxygen as among the most valuable of the agents available for the treatment of pulmonary emphysema—." In their hands, there is little question that oxygen therapy—by which they mean gradually increasing concentrations of inspired oxygen—is indicated because of its efficacy and safety. However, it may well be that relatively minute details of management, which are difficult to teach except by example, cannot be given in the text because they are so difficult to convey in writing. The reviewer feels strongly that oxygen therapy by any but very experienced individuals with excellent equipment, a well-trained nursing staff and fairly complete laboratory facilities can be, and frequently is, a very hazardous procedure. The text does not convey such an impression to the reviewer.

Otherwise, the first half of the book contains much clinical and physiological information about pulmonary emphysema that will be extremely valuable to all physicians who are faced with the problem in any of its varied aspects.

The second half of the book consists of a series of articles by students of pulmonary emphysema whose research and writings emphasize the laboratory and investigative aspects of the syndrome. All of the articles are good; some are outstanding—outstanding because they authoritatively summarize in readable fashion the results of many laboratory studies and much medical literature.

If the book deserves adverse criticism, and the reviewer believes it does, it is not because the content of any one monograph is lacking. Rather, the book portrays a very incomplete picture of pulmonary emphysema. For instance, the index does not list "Diagnosis," and diagnostics are largely ignored. This is especially true of the roentgenologic aspects of emphysema. Also, no real effort is given to presenting a picture of the pathogenesis and natural history of pulmonary emphysema in one section, labeled as such.

This lack of diagnostic and pathogenetic discussion makes it seem that one might be confronted with a patient bearing the label, "Pulmonary Emphysema," as if this were a well delineated, well understood syndrome.

A second major criticism might be that the laboratory has been made to serve the clinic and substantiate the clinician's ideas rather than providing the clinician with leads and ideas gleaned from basic investigation of the disease. Stated differently: It is currently impossible to make a clinical diagnosis of emphysema as the condition is described in pathology texts. And, moreover, emphysematous changes in the lungs probably do not, of themselves, lead to serious disability. However, chronic airway obstruction, which almost always precedes and frequently results in emphysematous changes, *can* be diagnosed qualitatively with considerable certainty and quantitatively with considerable precision.

An understanding of the pathophysiology of chronic generalized airway obstruction is emerging from studies such as are summarized in the articles by Alexander, Cherniak, Dayman, Fishman and Richards, and Riley. And, if generalized airway obstruction is the basic pathophysiologic defect in patients with "Pulmonary Emphysema," rational clinical management must begin with an understanding of obstructive disease.

In summary, this is a good collection of many excellent essays, but it does not convey a comprehensive picture of Pulmonary Emphysema.

B. W. A.

The Lung: Clinical Physiology and Pulmonary Function Tests (Based on the 1954 Beaumont Lecture). By JULIUS H. COMROE, JR., M.D., ROBERT E. FORSTER, II, M.D., ARTHUR B. DUBOIS, M.D., WILLIAM A. BRISCOE, M.D., and ELIZABETH CARLSEN, A.B. 210 pages; 23.5 × 15.5 cm. The Year Book Publishers, Inc., Chicago. 1955. Price, \$5.50.

Dr. Comroe and his colleagues at the University of Pennsylvania have spent many productive years studying respiratory physiology. The presentation of their findings to the medical public in concise, clear, nontechnical terms has been attained in this elegant volume, based on the 1954 Beaumont Lecture. The basic features of normal lung function are thoroughly reviewed, using diagrams to supplement text. Application of pulmonary function test data to clinical medicine is demonstrated by careful, pertinent analyses of many varied cases. An appendix contains some of the mathematics involved in respiratory physiology, and includes basic equations for those inclined toward calculations.

The internist has increasing need to understand applied pulmonary physiology. Dr. Comroe and his associated authors have produced a monograph which accomplishes its aim: "to explain in simple words and diagrams those aspects of pulmonary physiology that are important to clinical medicine." This book is strongly recommended to internists, surgeons, anesthesiologists and medical students.

J. E. C.

Virus and Rickettsial Diseases. 2nd Ed. By S. P. BEDSON, A. W. DOWNIE, F. O. MACCALLUM and C. H. STUART-HARRIS. 407 pages; 22 × 14.5 cm. Williams and Wilkins Company, Baltimore. 1955. Price, \$6.75.

This compact volume, written by four well-known English virologists, is admirably done. It presents a good selection of viral and rickettsial infections of medical importance in a brief, but highly informative, form. Basic aspects of the microbial agents, epidemiology of the infections and laboratory diagnostic methods are stressed along with control measures. Clinical and pathologic features have been minimized in accordance with the stated policy of the authors. Some chapters, such as the one on immunity in viral infections, are particularly outstanding. This second edition includes some new agents not known in 1950 and presents pertinent new information on agents like poliomyelitis and the Coxsackie group where recent advances have been significant. The book can be highly recommended for use by medical students, house officers, physicians and others who desire a readable, brief and authoritative introduction into a rapidly expanding field.

C. L. W., JR.

Venous Return. By GERHARD A. BRECHER, M.D., Ph.D. 148 pages; 26 × 17.5 cm. Grune & Stratton, New York. 1956. Price, \$6.75.

Early Greek medical records show that physicians long have speculated about factors influencing the return of venous blood to the heart. Many theories were

propounded to explain venous circulation. The testing of these theories has proceeded as technics for accurate measurement of venous pressures and flow were developed. From such investigations has come a more rational concept of venous return.

Dr. Brecher provides the reader with a comprehensive monograph. A brief historical section reviews major ideas about venous return. He emphasizes the peculiar hydraulic features of veins which make accurate measurements of pressure and flow more difficult than in the arterial system. Special instruments needed in this field of research are described and their uses demonstrated.

Two major themes are emphasized: (1) The influence of respiratory variations of intrathoracic pressure on venous return, and (2) the effects of the cardiac pump on venous flow. The text is amplified by numerous records of experimental data to emphasize certain points. Brevity, clarity, and simplicity of style characterize the writing. Frequent summaries clarify the implications of experimental data. The last few chapters present clinical applications of the concepts developed.

Dr. Brecher has produced a stimulating, clear book. Physicians and medical students will be interested in this material. Cardiologists, chest surgeons, and physiologists should find the contents especially rewarding.

J. E. C.

World Trends in Cardiology. Volume I—Cardiovascular Epidemiology. Edited by Keys and White. \$4.75; *Volume II—Cardiovascular Surgery.* Edited by Tausig and Cain. \$2.00; *Volume III—Blood Volume and Contractile Protein in Heart Muscle.* Edited by Cain. \$3.50; *Volume IV—Cardiovascular Diagnosis and Therapy.* Edited by Cain. \$3.85; *Volume V—Instrumental Methods in Cardiac Diagnosis.* Edited by Cain. \$3.85. Paul B. Hoeber, Inc., New York 16, N. Y. 1956.

In these five volumes are published selected papers from the Second World Congress of Cardiology, and the 27th Annual Scientific Sessions of the American Heart Association which were held in Washington, D. C., during the month of September 1954. There are made available in these five volumes many of the reports and panel discussions held at that time. Of necessity, many of the reports are brief. Over two years have passed since these meetings were held and some of the material is therefore dated. The illustrations are for the most part excellent although they frequently suffer because of inadequate legends.

These volumes make available material which would otherwise have escaped publication since the presentations were so often parts of panel discussions. To anyone interested in cardiology they are valuable as reference volumes for specific subjects and, what is probably more important, they furnish an opportunity to study the remarks of many of the leading authorities in the world on controversial subjects.

L. S.

Endogenous Uveitis. By ALAN C. WOODS, M.D. 303 pages; 26 × 18 cm. The Williams & Wilkins Co., Baltimore. 1956. Price, \$12.50.

This volume, by an author who has made the subject a lifetime study, is exhaustive in scope. The material is well organized and is presented in a clear, easily read style.

Chapter I deals with nomenclature, classification, and pathogenesis; chapter II the clinical picture and pathology of granulomatous and nongranulomatous uveitis; chapter III etiologic diagnosis of uveitis; and chapter IV the treatment of uveitis.

The volume is very nicely printed, the illustrations, particularly those in color, are excellent.

Certainly this work is a valuable contribution in the field of ophthalmology, and while of greatest interest to the student and the ophthalmologist, the internist, often called upon for aid in determining the etiology of uveitis, will find chapter III, in addition to suggestions of the referring ophthalmologist, a valuable guide in this endeavor.

H. F. G.

Congenital Anomalies of the Viscera: Their Embryological Basis. By J. LEWIS BREMER, M.D. 202 pages; 24 × 15.5 cm. Harvard University Press, Cambridge. 1957. Price, \$5.00.

This book presents an interesting departure from embryology per se. With each organ or system the normal embryology is briefly reviewed before presenting congenital malformations. Numerous simple black-and-white illustrations serve to correlate the normal with abnormal developmental anomalies. Included are chapters on the nose, mouth and face, pharynx and neck, intestinal tract, liver and pancreas, urinary and reproductive systems, as well as four chapters on the heart and aortic arches. These uncommon anomalies are encountered by house officers and practicing physicians. This book should serve as an excellent, quick and informative review.

HARRY C. HULL, M.D.

The Doctor in Personal Injury Cases. By HAROLD A. LIEBENSON. 123 pages; 18.5 × 12 cm. The Year Book Publishers, Inc., Chicago, Illinois. 1956. Price, \$4.00.

This is a pocket edition containing an excellent introduction for a physician to personal injury litigation. In its nine chapters, it provides worthwhile information concerning the doctor's importance in such litigation, the essential elements and the proper preparation of medical reports, basic information about the operation of the courts and the physician's conduct in trial. There is a thorough explanation of the significance of opinion evidence and the use of hypothetical questions. Good advice is given concerning the manner of a physician's testimony, the preparation necessary therefor and the physician's conduct while under cross-examination. The section on common errors in cross-examination and common questions the physician meets, with particular emphasis on those which are intended to confuse or create hostility on the part of the witness, is extremely valuable.

The book is easy reading and is highly recommended to any physician concerned with testimony in court in any type of case.

R. S. F.

BOOKS RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advisory Group on Veterinary Public Health: Report. World Health Organization Technical Report Series No. 111. 26 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Anatomie Des Menschen. I. Teil: Allgemeine Anatomie/Rücken/Bauch/Becken/Bein. By PROF. DR. MED. ET PHIL. A. WALDEYER. 369 pages; 24.5 × 18 cm. 1957. Walter de Gruyter & Co., Berlin. Price, Ganzleinen DM 38,—.

- Challenges to Contemporary Medicine. Number Six, Bampton Lectures in America, Delivered at Columbia University, 1953.* By ALAN GREGG, Vice President Emeritus of the Rockefeller Foundation. 120 pages; 21 × 14 cm. 1956. Columbia University Press, New York. Price, \$3.00.
- Clinical Use of Radioisotopes.* By WILLIAM H. BEIERWALTES, M.D., Associate Professor of Internal Medicine and Coördinator, Clinical Radioisotope Unit, University Hospital, Ann Arbor; PHILIP C. JOHNSON, M.D., Assistant Professor of Internal Medicine and Chief, Radioisotope Unit, Veterans Administration Hospital, University of Oklahoma Medical School, Oklahoma City; and ARTHUR J. SOLARI, B.S., M.S. (Physics), Instructor in Radiation Physics, Department of Radiology, Radiation Physicist for Clinical Radioisotope Unit and Kresge Research Isotope Unit, University Hospital, Ann Arbor. 456 pages; 24 × 16 cm. 1957. W. B. Saunders Company, Philadelphia. Price, \$11.50.
- Contemporary Rheumatology: Proceedings of the Third European Rheumatology Congress, The Hague-Scheveningen, 1955.* Honorary Editors: J. GOSLINGS, Professor of Rheumatology, University of Leyden; and H. VAN SWAAY, Rheumatologist, Deaconess Hospital "Bronovo," The Hague; under the auspices of The Congress Committee. 683 pages; 26 × 17 cm. 1956. Elsevier Publishing Company, New York. Price, \$15.00.
- Coronary Heart Disease: Angina Pectoris; Myocardial Infarction.* By MILTON PLOTZ, M.D., F.A.C.P., Clinical Associate Professor of Medicine, State University of New York, Medical Center at New York, etc.; foreword by WILLIAM DICK, M.D. 353 pages; 26 × 18 cm. 1957. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$12.00.
- Cortico-Surrénale et Diabète Humain: Relations entre le Diabète Stéroïdien et le Diabète Ordinaire.* By P. BASTENIE, with the collaboration of J. CHRISTOPHE, V. CONARD, J. R. M. FRANCKSON, W. GEPTS, R. DE MEUTTER, J. PIRART, R. TAGNON and M. VERBIEST. 506 pages; 25 × 17 cm. 1956. Masson et Cie., Paris. Price, 4,000 fr.
- Drugs in Current Use, 1957.* Edited by WALTER MODELL, M.D., F.A.C.P., Associate Professor, Clinical Pharmacology, Cornell University Medical College. 152 pages; 21 × 14 cm. (paper-bound). 1957. Springer Publishing Company, Inc., New York. Price, \$2.00.
- The Importance of Overweight.* By HILDE BRUCH, M.D. 438 pages; 21.5 × 14.5 cm. 1957. W. W. Norton & Company, Inc., New York. Price, \$5.95.
- Pediatric Cardiology.* By ALEXANDER S. NADAS, M.D., F.A.A.P., Assistant Clinical Professor of Pediatrics, Harvard Medical School, etc. 587 pages; 24.5 × 16 cm. 1957. W. B. Saunders Company, Philadelphia. Price, \$12.00.
- The Physician-Writer's Book: Tricks of the Trade of Medical Writing.* By RICHARD M. HEWITT, A.M., M.D., Senior Consultant, Section of Publications, the Mayo Clinic, etc. 415 pages; 24 × 15.5 cm. 1957. W. B. Saunders Company, Philadelphia. Price, \$9.00.
- La Polyarthrite Chronique Évolutive.* By L. ISEMEIN and A.-M. FOURNIER, with the collaboration of P. CIAUDO, A. TRIFAUD and Cl. COURTIEUX; preface by PROFESSOR F. COSTE. 315 pages; 25 × 17 cm. (paper-bound). 1956. Masson et Cie., Paris. Price, 3,200 fr.

- Positioning in Radiography.* 7th Ed. By K. C. CLARK, M.B.E., F.S.R., Honorary Fellow and Past President, Society of Radiographers, etc. 655 pages; 30.5 × 23 cm. 1956. Grune & Stratton, New York. Price, \$29.00.
- Proceedings of the Third National Cancer Conference, Detroit, Michigan, June 4-6, 1956.* Sponsored by AMERICAN CANCER SOCIETY, INC., and NATIONAL CANCER INSTITUTE, U. S. PUBLIC HEALTH SERVICE. 961 pages; 26 × 18.5 cm. 1957. J. B. Lippincott Company, Philadelphia. Price, \$9.00.
- Toxemia of Pregnancy: Report of the First Ross Obstetric Research Conference.* 79 pages; 22.5 × 15 cm. (paper-bound). 1956. Issued by Ross Laboratories (formerly M & R Laboratories), Columbus, Ohio. Available on request.
- Ultramicro Methods for Clinical Laboratories.* By EDWIN M. KNIGHTS, JR., M.D. Associate Pathologist, Director of Clinical Pathology and Blood Bank; RODERICK P. MACDONALD, Ph.D., Director of Clinical Chemistry and Research Advisor; and JAAN PLOOMPUI, Chief, Division of Ultramicro Chemistry and Research Associate, all of Harper Hospital, Detroit. 128 pages; 22.5 × 14 cm. 1957. Grune & Stratton, New York. Price, \$4.75.

COLLEGE NEWS NOTES

NEW LIFE MEMBERS

The College acknowledges with pleasure the following Fellows as new Life Members:

Dr. Theodore I. Bauer, Lansing, Mich.
Dr. Samuel Benjamin, Washington, D. C.
Dr. Gordon N. Best, Council Bluffs, Iowa
Dr. Marion A. Blankenhorn, Cincinnati, Ohio
Dr. Donald W. Bortz, Greensburg, Pa.
Dr. J. Antrim Crellin, Philadelphia, Pa.
Dr. Robert W. Currie, Indianapolis, Ind.
Dr. Edwin M. Duvall, Long Beach, Calif.
Dr. Lewis B. Flinn, Wilmington, Del.
Dr. Aaron P. Gewanter, Somerville, N. J.
Dr. Wayne Gordon, Billings, Mont.
Dr. Leland Hawkins, Los Angeles, Calif.
Dr. Herman S. Hoffman, Washington, D. C.
Dr. Lester Hollander, Pittsburgh, Pa.
Dr. J. Kenneth Karr, Milwaukee, Wis.
Dr. Luther W. Kelly, Charlotte, N. C.
Dr. Louis I. Kramer, Providence, R. I.
Dr. Seaborn J. Lewis, Beaumont, Tex.
Dr. Alfred R. Masten, Denver, Colo.
Dr. Desmond F. McGuire, East Chicago, Ind.
Dr. Edgar M. McPeak, Houston, Tex.
Dr. Timothy R. Murphy, Milwaukee, Wis.
Dr. Edward A. Newman, Chicago, Ill.
Dr. George W. Parson, Texarkana, Tex.
Dr. Hilton S. Read, Atlantic City, N. J.
Dr. Edwin J. Rose, Chevy Chase, Md.
Dr. Henry L. Smith, Detroit, Mich.
Dr. Robert M. Stecher, Cleveland, Ohio
Dr. Lewis W. Woodruff, Joliet, Ill.

COMING MEDICAL CONVENTIONS

American

American Medical Association, New York, N. Y., June 3-7, 1957
American Public Health Association, Cleveland, Ohio, November 11-15, 1957
American Rheumatism Association, Toronto, Ont., Can., June 23-28, 1957
American Society of Clinical Pathologists, New Orleans, La., Sept. 29-Oct. 4, 1957
American Society of Tropical Medicine & Hygiene, Philadelphia, Pa., Oct. 30-Nov. 2, 1957
Association of American Medical Colleges, Atlantic City, N. J., October 21-23, 1957
Association of American Physicians, Atlantic City, N. J., May 7-8, 1957
Association of Military Surgeons of U. S., Washington, D. C., October 28-30, 1957
College of American Pathologists, New Orleans, Sept. 29-Oct. 4, 1957
Interstate Postgraduate Medical Association of North America, Chicago, Ill., Sept. 29-Oct. 3, 1957

National Tuberculosis Association, Kansas City, Mo., May 5-10, 1957
 Radiological Society of North America, Chicago, Ill., November 17-22, 1957
 Southern Medical Association, Miami Beach, Fla., November 11-14, 1957
 World Medical Association, Istanbul, Turkey, Sept. 29-Oct. 5, 1957

Foreign and International

CANADIAN MEDICAL ASSOCIATION, Edmonton, Alberta, Canada, June 17-21, 1957. Dr. A. D. Kelly, 150 St. George St., Toronto, Ont., Canada, General Secretary.
 INTER-AMERICAN CONGRESS OF PAN AMERICAN MEDICAL ASSOCIATION, Mexico City, Mexico, Nov. 18-22, 1957. Dr. Joseph J. Eller, 745 Fifth Ave., New York 22, N. Y., U. S. A., Executive Director.
 INTER-AMERICAN MEDICAL CONVENTION, Hotel El Panama, City, Republic of Panama, April 3-5, 1957. Dr. William T. Bailey, Medical Association of the Isthmian Canal Zone, Box E, Balboa Heights, Canal Zone, Chairman, Publicity Committee.
 INTERNATIONAL CONGRESS OF CLINICAL PATHOLOGY, Brussels, Belgium, July 15-20, 1957. Prof. M. Welsch, Service de Bacteriologie et de Parasitologie, Universite de Liege, 32 Blvd., de la Constitution, Liege, Belgium, Secretary General.
 INTERNATIONAL CONGRESS OF DERMATOLOGY, Stockholm, Sweden, July 31-Aug. 6, 1957. Dr. C. H. Floden, Karolinska, Sjukhuset, Hudliniken, Stockholm 60, Sweden, Secretary General.
 INTERNATIONAL CONGRESS OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY, Brussels, Belgium, July 21-28, 1957. For information address: Dr. R. G. Bickford, Mayo Clinic, Rochester, Minn., U. S. A.
 INTERNATIONAL CONGRESS OF EUROPEAN SOCIETY OF HAEMATOLOGY, Copenhagen, Denmark, Aug. 26-31, 1957. Dr. Aage Videbask, Blegdamsvej 11, Copenhagen, Denmark, Secretary General.

III INTERNATIONAL CONGRESS OF ALLERGOLOGY

Paris, France, October 19-25, 1958

The Scientific Program will consist of Symposia by international authorities in the field and related fields of Allergy. There will be general sessions and sectional meetings. Those in the United States and Canada wishing to present papers should submit their titles and brief abstracts to Dr. S. M. Feinberg, F.A.C.P., President, International Association of Allergology, Northwestern University Medical School, 303 East Chicago Avenue, Chicago 11, Illinois. Physicians from other countries should submit their titles and abstracts to Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris VII^e, France.

For general information about the Congress, address either Dr. Feinberg or Dr. José Quintero Fossas, Secretary-General, Paseo 313, Vedado, Havana, Cuba.

FELLOWSHIPS IN PSYCHIATRY

The American Psychiatric Association has recently announced the award of fourteen Smith, Kline & French Foundation Fellowships in Psychiatry. Applications for future Fellowships should be sent to the Fellowships Committee, American Psychiatric Association, P. O. Box 7929, Philadelphia, Pa.

Seven main types of Smith, Kline & French Foundation Scholarships are available:

(1) Support for advanced training for full-time staff psychiatrists of public mental hospitals and schools for the retarded.

- (2) Awards to hospitals for visiting lectureships and for teaching fellowships.
- (3) Support for medical schools, teaching centers, etc., for extension training programs.
- (4) Student fellowships to encourage talented medical students to engage in summer activities in psychiatry.
- (5) Medical fellowships to encourage broadened skill in psychiatric problems of everyday practice by physicians other than psychiatrists.
- (6) Foreign scholar lectureships to bring outstanding men to the United States.
- (7) Residency training fellowships under unusual circumstances.

AMERICAN BOARD OF INTERNAL MEDICINE ORAL EXAMINATION

To complete the schedule of examinations of this Board as recently published in this journal, the Board announces the oral examination for candidates on the West Coast at Los Angeles, Calif., on Sept. 11-14, 1957.

UNIVERSITY OF MICHIGAN REGIONAL CONFERENCE ON HYPERTENSION

A Regional Conference on Hypertension will take place at Ann Arbor, Mich., June 7-8, 1957, in recognition of the 25th Anniversary of the first production of Experimental Renal Hypertension by Dr. Harry Goldblatt. Reports will be presented on the Basic Mechanisms of Renal Hypertension, including adrenal, neurogenic and renoprival aspects. Many participants will be distinguished men from abroad. Those desiring to attend are urged to write well in advance for information and reservations to Dr. John Sheldon, F.A.C.P., Director, Department of Postgraduate Medicine, University of Michigan Medical School, University Hospital, Ann Arbor, Mich.

THE AMERICAN JOURNAL OF CARDIOLOGY

The American College of Cardiology is initiating a new journal, THE AMERICAN JOURNAL OF CARDIOLOGY. Dr. Simon Dack, F.A.C.P., New York, N. Y., is the Editor.

NEW STATE SOCIETIES OF INTERNAL MEDICINE

The Michigan Society of Internal Medicine was recently organized in Lansing, Mich., February 23, 1957. All of the founding members are Diplomates of the American Board of Internal Medicine or members of the American College of Physicians. The group will affiliate with the American Society of Internal Medicine. Dr. James W. Hall, F.A.C.P., Traverse City, is President; Dr. Michael Kozonis, (Associate), Pontiac, is Vice President; and Dr. Ross V. Taylor, F.A.C.P., Jackson, is the Secretary-Treasurer. All of the charter members are members of the American College of Physicians. The annual meeting of this society will be held each Autumn concomitantly with the Michigan Regional Meeting of the American College of Physicians.

Several internists from throughout the State of Pennsylvania met in Harrisburg, Pa., February 16, 1957, and unanimously agreed to form a Pennsylvania Society of Internal Medicine. This group will be primarily interested in the socio-economic aspects of the practice of internal medicine as they affect the internist and his patients. An Interim Committee, which includes a number of members of the American College of Physicians, was appointed and directed to formulate By-Laws, accept applications for membership, etc.

OMAHA MID-WEST CLINICAL SOCIETY ANNUAL MEETING

The Twenty-Fifth Annual Assembly will be held at the Sheraton-Fontenelle Hotel, Omaha, Nebr., November 4, 5, 6, and 7, 1957.

SOCIETY OF NUCLEAR MEDICINE ANNUAL MEETING

The fourth annual meeting of the Society of Nuclear Medicine will be held June 20-23, 1957, at the Skirvin Hotel, Oklahoma City, Okla. A program of outstanding papers, speakers and exhibits is planned. Additional information can be secured from Robert W. Lackey, M.D., Secretary, 452 Metropolitan Bldg., Denver, Colo.

NEW YORK PSYCHOSOMATIC FORUM MEETING

The New York Psychosomatic Forum will be held on Friday evening, 8:30 P.M., June 7, 1957, at the New York State Psychiatric Institute auditorium. The topic will be "Contributions to Patterns of Research in Psychosomatic Medicine." Speakers will include Fred Brown, Ph.D., Lawrence S. Kubie, M.D., and Herman A. Witkin, Ph.D. The speakers will stress future possibilities for research and its practical relationships to clinical approaches.

THIRD INTERNATIONAL MEDICAL-SURGICAL MEETINGS

Turin, Italy, will be host, June 1-9, 1957, to physicians, surgeons and specialists in all fields of the medical sciences for the Third International Medical-Surgical Meetings. During the nine days of the Meetings illustrious personalities in the field of medical science will take part in four International Congresses, seven National Congresses, ten Symposia and many other meetings. Among the many features will be the International Congress on Nuclear Medicine, the International Congress on Photobiology, the International Congress on Problems of Goitre, a national congress on gastro-enterology, and a symposium on artificial heart-lung machines. A scientific exhibit will be held in conjunction with the meetings.

Complete details can be secured from the Segreteria Generale, Minerva Medica, Torino, Italy.

NEW YORK UNIVERSITY POSTGRADUATE COURSES

Two new full-time courses on the management of chronic kidney disease and of hypertension are to be given by the New York University Post-Graduate Medical School from June 24-27, 1957.

The management of chronic kidney disease (June 24-25), under the direction of Dr. Lawrence G. Wesson, F.A.C.P., will deal with the selection and interpretation of clinically available tests for the estimation of renal function. The advantages and disadvantages of each test will be considered.

The management of hypertension (June 26-27), under the direction of Dr. J. Marion Bryant, will be concerned with the presentation and demonstrations of the following: brief summary of etiologic theories, psychological factors, natural course, relative significance of blood pressure levels, etc.

Information can be obtained from the Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Ave., New York City 16.

FELLOWSHIPS AND SCHOLARSHIPS OFFERED BY THE NATIONAL FOUNDATION
FOR INFANTILE PARALYSIS

Many fellowships and scholarships are available through the Division of Professional Education, National Foundation for Infantile Paralysis, 301 East 42nd Street, New York 17, N. Y. Interested individuals may obtain full data by writing to the Foundation.

FELLOWSHIPS IN RESEARCH AND CLINICAL ALLERGY

The Board of Trustees of the American Foundation for Allergic Diseases announces the availability of three Fellowships in Research and Clinical Allergy for a period of two years each, carrying a stipend of \$4,500 for the first year, \$4,750 for the second year, and a total of \$750 for laboratory and traveling expenses during the two-year period. Funds for these fellowships have been made available by Mr. John D. Rockefeller, Jr., in a grant to the Foundation.

It is the hope of the Foundation that the recipients will be stimulated to enter the field of research in allergy and will be equipped to teach others. Applications should be made to one of the following investigators: Dr. Frederick G. Germuth, Jr., Associate Professor of Pathology, The Johns Hopkins University Medical School, Baltimore 5, Md.; Dr. Colin M. MacLeod, Professor of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia 4, Pa.; Dr. Herman N. Eisen, Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

The 23rd Annual Meeting of the American College of Chest Physicians will be held at the Hotel Commodore, New York City, May 29-June 2, 1957. The program will cover all aspects of heart and lung diseases. Copies of the program are available through the Executive Offices of the society, 112 East Chestnut St., Chicago 11, Ill.

The Schools of Medicine of the University of Pennsylvania were the host to the Fourth Grand Rounds, telecast nationally from the University Hospital on March 27. A panel of distinguished clinicians engaged in extemporaneous discussion of "Pre-Malignant and Malignant Lesions of the Breast and Colon."

Fourteen June graduates of medical schools approved by the American Medical Association will report for duty at the U. S. Army Hospital, Fort Benning, Ga., July 1, 1957, to inaugurate the first internships yet instituted for the Army's Class I hospitals. This will be a "pilot" program directed towards the introduction of such training in other hospitals of this classification.

Extension of the intern program of the Army Medical Service to other Class I hospitals is hoped for as a result of the pilot study. Applications for Army medical internships have exceeded by far in recent years the number of openings available at the Army's named teaching hospitals. This has brought about a need to expand the intern training programs to accommodate more of the young physicians interested in Army professional training.

The Department of Health, Education, and Welfare announces that the Seventh Annual Research Equipment Exhibit and Instrument Symposium is to be held from May 13-16 at the National Institutes of Health, Bethesda, Maryland.

Approximately 100 exhibitors will display one quarter million dollars' worth of the latest research instrumentation. Certain equipment, to be viewed publicly for the first time, should prove of interest to technical as well as professional persons in the field of science.

This annual display has become the largest concentration of research equipment in the United States, and provides a unique opportunity for qualified persons to view the instruments and to exchange information with the manufacturers' technical representatives who will be on hand.

The exhibits will be open daily at 11:30 a.m. and will close at 6:00 p.m. on May 13 and 16 and at 9:00 p.m. on May 14 and 15. Instructional sessions demonstrating six new instruments for research will be held, and a series of motion pictures dealing with scientific subjects will be shown.

Members of the College who may be interested are invited to attend.

Dr. Howard Wakefield, F.A.C.P., Chicago, has been reelected Chairman of the Residency Review Committee on Internal Medicine. This Committee is made up of representatives from the American Medical Association, the American Board of Internal Medicine, and the American College of Physicians.

Dr. George A. Perera, New York City, has been elected a member of the American Board of Internal Medicine to succeed Dr. Claude Forkner, F.A.C.P., of Boston, Mass. Dr. Perera is an appointee of the Section on Medicine of the American Medical Association.

Dr. Henry J. Tumen, F.A.C.P., Philadelphia, Pa., has been appointed consultant in gastroenterology to the Walter Reed Army Hospital, Washington, D. C.

Dr. Chris J. D. Zarafonitis, F.A.C.P., Clinical Professor of Medicine at Temple University Medical Center, participated in the 53rd Annual Conference on Medical Education and Licensure in Chicago, February 9-10. He addressed a meeting of the Medical Education for National Defense Coördinators at the February 10 session on methods of introducing the MEND program to the faculty of a medical school. Dr. Zarafonitis is MEND coördinator for the Temple University School of Medicine.

The American Goiter Association will hold its 1957 meeting at Hotel Statler, New York City, May 28-30, 1957. The program will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland.

The International Symposium of Clinical Psychopharmacology will be held in Milan, Italy, May 9, 10, 11, 1957.

The Ciba Pharmaceutical Products Company of Summit, N. J., has published for general distribution to the medical profession the panel entitled, "Clinical Endocrinology for the Internist," which was given before the 37th Annual Session of the American College of Physicians at Los Angeles, Calif., April 17, 1956. This panel was published after editing by the panelists and with the approval of the American College of Physicians, and is available on request to the publishers.

Dr. Mayer A. Green, F.A.C.P., Pittsburgh, Pa., was a participant in the first seminar for regional consultants of the Jewish National Home for Asthmatic Children at Denver, January 30-31, 1957.

Dr. Green presented a paper entitled "The Role of the Generalist in Allergy," on February 15 before the Hawaiian Academy of Medicine at the Honolulu Session of the American Academy of Allergy Convention.

Dr. Ward Darley, F.A.C.P., Evanston, Ill., resigned as President of the University of Colorado in December, 1956. Dr. Darley is now Executive Director for the Association of American Medical Colleges.

Dr. John M. McMahon, F.A.C.P., Bessemer, Ala., was recently elected a Trustee of the American College of Gastroenterology and to the Editorial Council of the American Journal of Gastroenterology.

Dr. William Dameshek, F.A.C.P., Boston, Mass., delivered the Fifth Annual Emanuel B. Schoenbach Memorial Lecture at the Maimonides Hospital, Brooklyn, N. Y., on April 25, 1957. Dr. Dameshek's paper was entitled "Polycythemia and Related States."

Dr. Herbert Berger, F.A.C.P., Staten Island, N. Y., President of the Blood Bank Association of New York State, addressed the California Blood Bank System of the California Medical Association in San Francisco on February 23, 1957. Dr. Berger spoke on the rôle of state medical associations in blood banking.

Participants in the Panel Discussions program, held March 4-5, 1957, to commemorate the Diamond Jubilee of the University Hospital of the New York University-Bellevue Medical Center, were the following Fellows of the College: Francis J. Braceland, Hartford, Conn.; Howard A. Rusk, New York City; Chester S. Keefer, Boston, Mass.; C. P. Rhoads, New York City; and Irvine H. Page, Cleveland.

On the Convocation Steering Committee were George E. Armstrong, F.A.C.P., Clarence E. de la Chapelle, F.A.C.P., William N. Hubbard, Jr., (Associate), and Charles A. Poindexter, F.A.C.P., all of New York City.

THE AMERICAN COLLEGE OF PHYSICIANS
CONDENSED REPORT
MINUTES OF THE BOARD OF REGENTS
PHILADELPHIA, PA.
November 10-11, 1956

Attendance:

23 Regents, 18 Committee Chairmen or special representatives; President Walter L. Palmer presiding.

Communications:

- (1) Grant of \$43,100.00 received from National Institutes of Health, Department of Health, Education and Welfare, toward the ACP research project, Study of Hospital Standards in Medicine;
- (2) Mead Johnson & Company will defray cost of providing formal certificates to all Mead Johnson Graduate Residency Scholars;
- (3) Dr. William J. Erdman, II, (Associate), Philadelphia, appointed ACP representative on the Advisory Committee on Physical Therapy Education, Council on Medical Education and Hospitals, AMA;
- (4) ACP contributed \$100.00 to the National Society for Medical Research;
- (5) Stengel-Martin Portrait completed and hung in the College Headquarters;
- (6) The Regents approved the request of the American Heart Association to hold a two-day clinical session at Atlantic City, just prior to opening of the ACP Annual Session, 1958.

Secretary-General's Report:

Deaths of 1 Master, 59 Fellows, 7 Associates, since last meeting of the Board; 14 additional Life Members, since last meeting of the Board (in both cases, names officially spread in the Minutes).

A progress report submitted on the American Society of Internal Medicine.

A formal certificate adopted for issuance to retiring General Chairmen of Annual Sessions, with covering appropriation for cost.

Committee Reports:

- (1) *General Chairman, Dr. Richard P. Stetson, Boston Annual Session*, covering all details.

RESOLVED, that non-member guests of the College who participate in the Panel Discussions and in the Clinical Conferences shall have their expenses defrayed as non-members on the program of General Sessions, Morning Lectures and Symposia.

RESOLVED, that the budget for the General Chairman's publicity expenses be increased from \$1,500.00 to \$3,500.00.

- (2) *Chairman, Consulting Committee on Annual Sessions:*

Detailed report on selection of speakers through participation of Committee on Educational Policy; announcement regarding distinguished foreign guests who were invited to participate in the Boston Annual Session.

(3) *Regarding Convocation:*

RESOLVED, that the Convocational Lecture or Oration be omitted at the Boston Session, and that the President shall give his Annual Address, concluding same with his charge to the new Fellows.

(4) *Co-Operative Committee with the Royal Colleges:*

RESOLVED, that two silver salvers, with an appropriate case and suitably engraved silver plate, shall be purchased and presented to the Royal College of Physicians of London . . . during the 38th Annual Session of the College at Boston, April, 1957 (appropriation up to \$500.00 made).

(5) *Committee on Latin-American Fellowships:*

Report on personal interviews, placement arrangements and evaluation of progress of each fellow.

(6) *Committee on Fellowships and Scholarships:*

Nominations of candidates for Brower Traveling Scholarships, Bowes Traveling Scholarship, Thompson Traveling Scholarship in Endocrinology, Mead Johnson Graduate Residency Scholarships; Research Fellowships and Alfred Stengel Research Fellow, with alternates—formally approved by Regents, with total appropriation increased to \$25,700.00 for 1957-58.

(7) *Joint Commission on Accreditation of Hospitals:*

Report on activities; annual budget, \$105,000.00; ACP heretofore provides about \$34,000.00, half for administrative expenses and half for an ACP surveyor; number of ACP surveyors increased to two, with budget increase for 1957 to \$49,000.00.

(8) *Committee on Credentials:*

276 nominees elected to Associateship; 154 nominees elected to Fellowship.

(9) *Committee on Academic Regalia:*

Specific hoods approved for regular Masters and for Masters who previously served as Presidents of the College.

Regents authorized appointment of an Assistant Marshal.

Secretary-General, the Marshal and Executive Secretary authorized to edit citations for the Convocation—recommend that citations not exceed one hundred words.

RESOLVED, that past Presidents of the College, if seated on the stage at any subsequent Convocation of the College, shall wear their Presidential regalia, presented to them at the beginning of their Presidencies.

(10) *Committee on Masterships:*

Presentation of nominees for Masterships; approved by Regents:

Dr. William B. Castle, Boston
Dr. Cyrus C. Sturgis, Ann Arbor
Dr. Russell M. Wilder, Rochester

Presentation of nominees for Honorary Fellowships; approved by Regents:

Dr. Edward G. Sayers, Auckland, New Zealand
The Right Honorable The Lord Cohen of Birkenhead, Liverpool, England

Regents and Governors to be solicited to offer suggestions of nominees for Master-ships; procedure adopted to send a letter to each such officer, citing the qualifications necessary and requesting suggestions of nominees, said letter to be sent from the Executive Offices two months in advance of the autumn meeting of the Regents; letters to bear signature of the Chairman of the Committee.

Executive Offices instructed to prepare list of Masters and list of Honorary Fellows in chronological order of their election for incorporation in the next edition of the College Directory.

(11) *Committee on Awards:*

From nominees presented, the following were formally chosen by the Board of Regents:

Dr. Cecil J. Watson, F.A.C.P., Minneapolis—John Phillips Memorial Award	
Dr. Caroline Bedell Thomas, F.A.C.P., Baltimore,	} Joint Recipients, James D. Bruce Memorial Award
and	
Dr. Alvin Frederick Coburn, Chappaqua, N. Y.	
Dr. William D. Stroud, F.A.C.P., Philadelphia—Alfred Stengel Memorial Award	

RESOLVED, that the Committee on Awards shall be and is herewith authorized to review all of the requirements for the various ACP awards, and be instructed to make a recommendation to the Board of Regents at the April, 1957, meeting, with regard to amendments or changes in the present setup.

(12) *Committee on International Relations:*

Terms of reference previously clearly defined, but suggested purposes shall include:

- (a) Exploring the question of finding funds to bring to the Annual Sessions of the College distinguished foreign medical guests;
- (b) To enable the College to put into operation a plan to bring to the United States and Canada recent graduates of medical schools in Great Britain, Australia and New Zealand for postgraduate training;
- (c) To arrange for interchange of lecturers of professorial rank among various English speaking countries.

RESOLVED, that the above terms of reference for this Committee be approved; that it be recommended that beginning in 1958 the College may be able to afford at its own expense to bring three distinguished foreign speakers to each Annual Session (including travel expenses and a generous per diem allowance).

RESOLVED, that the matter referring to having up to three foreign guests, beginning at the 1958 Session at College expense, be referred back to the Committee on International Relations for further study, for consultation with the Committee on Finance, and then for reconsideration by the Regents in April, 1957.

RESOLVED, that proposals "(b)" and "(c)" be also further studied and explored.

A resolution, providing that the Regents give authorization in principle to the use of funds from pharmaceutical or other manufacturing houses for the purpose of inviting guests to the annual meetings, the number and choice to be left to the discretion of the President and his Advisory Committee, was defeated.

RESOLVED, that the plan of not accepting funds for named lectureships from pharmaceutical houses shall after 1957 apply also to any lectureship now existent.

RESOLVED, that the possibility of establishing a general fund through contributions by pharmaceutical houses, foundations, et al., for the purposes heretofore discussed, be referred to the Committee on International Relations for study.

(13) *Committee on Advertising and Technical Exhibits:*

A detailed report on growth of advertising, growth of advertising income, methods of accepting advertising, number of pages, number of paid pages of advertising and circulation of the *ANNALS*;

Discussion of complimentary exhibits by medical and health agencies; details concerning the Technical Exhibit at the Boston Annual Session, 1957;

A proposal approved to increase advertising rates, based on growth of circulation, was approved for January 1, 1958.

(14) *Committee on Cancer:*

First, a report on progress of the Cancer Committee of the ACS, with which the ACP co-operates through its official appointee, Dr. Samuel G. Taylor, III; a report on the Central Tumor Registries and the Third International Cancer Congress. Following objectives adopted by ACP Committee on Cancer for a long-range program:

- (1) Stimulate the internist in improving his knowledge in (a) cancer diagnosis in the early state of disease; (b) the selection of the proper definitive therapy, be it surgical, radiotherapeutic or medical; (c) the best available therapy in disseminated disease; (d) palliative procedures in terminal disease.
- (2) Co-operate with other national organizations in the field of cancer for the dissemination of knowledge, improvement in service to the cancer patient and collection of clinical data of value in furthering the knowledge on cancer.
- (3) Encourage research in the field of cancer, especially in the field of chemotherapy, hormone therapy, immune mechanisms and growth phenomena.

Committee recorded following recommendations:

- (1) That an inspired speaker be selected for a major address to the College at the next Annual Session on clarification of the role of the internist in the problem of neoplasia.
- (2) That more time be allotted to the problem of cancer diagnosis, therapy and research in the programs of the regional, national and postgraduate meetings.
- (3) That a series of well-selected articles on early diagnosis, modes of therapy, course and end results of cancer in various sites be published consecutively in the *ANNALS OF INTERNAL MEDICINE*, with fortification by editorial comment so the internist can form his own opinion as to the advisability of subjecting his patient to various forms of therapy recommended by surgical or radiological consultants.
- (4) That a list of available funds for cancer research, fellowship and trainee programs be published in the *ANNALS OF INTERNAL MEDICINE* periodically. A list of institutions offering good trainee programs in cancer should also be listed.

Committee recommended a pamphlet of chemotherapy in cancer be formulated for the approved Tumor Clinics and be done as a joint project of the Cancer Committees of the ACP and ACS, and not merely by consultation with certain members of the

Committee; also recommended that joint subcommittees of the two Cancer Committees should be formed as ad hoc committees when the need arises.

Dr. Harold Warwick, of Toronto, and Dr. R. Wayne Rundles, F.A.C.P., Durham, were added to the ACP Committee.

Steps were initiated to inform following organizations of the existence and objectives of the ACP Cancer Committee: National Cancer Institute, American Cancer Society, Damon Runyon Fund, American College of Surgeons, American College of Radiology and Association of American Pathologists.

(15) *The Bauerlein Governors' Survey:*

Report on the continuation of the Governors' survey or self appraisal of the College, by means of a questionnaire sent to non-member internists and College Associates in States of California, Nevada, Tennessee, Minnesota, and New York; 1,547 questionnaires went out; 904 replies received; 32% of replies were accompanied by written analytical statements; 50% of the Associates and 30% of the non-members answering questionnaire were in private practice; 5.2% of Associates and 3.1% of non-members were in full-time teaching; 6.6% of Associates and 4.9% of non-members were mixed in private practice and teaching.

Over 90% of Associates indicated their continued intention to qualify for Fellowship; 67% of non-members indicated their desire to qualify for College membership.

86.3% of Associates thought the College is fulfilling its obligation to internists; 11% of the Associates said "No"; 63.5% of non-members announced in the affirmative; 20.6% answered in the negative, and 15.9% had no opinion.

Opinion was divided, 50-50, as to whether the College should concern itself more with economic aspects of medicine.

A great host, 309 letters, discussing various features of the College would not permit of general summarization.

Recommendations of the Committee:

- (1) The College should not enter directly into the medical economic field.
- (2) The College should make an official investigation and close scrutiny of the purposes of the newly formed American Society of Internal Medicine.

Conclusion:

The survey reveals the high regard in which internists hold the educational opportunities which the College affords, with the hope that such will be continually expanded.

(16) *Residency Review Committee in Internal Medicine:*

Confederated effort by ACP, AMA and ABIM.

Chairman Howard Wakefield presented proposed organization and functions—(a) to stimulate improvement in every possible manner of residency and fellowship training in Internal Medicine in American medical institutions; (b) to prepare recommendations to the Council in Medical Education and Hospitals on revisions of the "Essentials" of an approved residency in Internal Medicine; (c) to evaluate residencies currently approved or subsequently submitted for approval; (d) to approve or disapprove residencies, with power to act for the three parent organizations; (e) to prepare a list of approved residencies in Internal Medicine.

(17) *American Occupational Therapy Association—Medical Advisory Council:*

Review of the work of this Council, had been impressive, with respect to character and purposes of the organization, its goals and ideals.

RESOLVED, that Dr. Howard Wakefield shall represent the College on this Council for a period of three years.

(18) Commission on Professional and Hospital Activities:

An extended report on progress by Dr. C. Wesley Eisele; a stable organization had been achieved; present organizational plan and By-Laws approved by four sponsoring organizations, the ACP, the ACS, the American Hospital Association and the Southwestern Michigan Hospital Council.

Names of official representatives from each organization recorded; details of Educational Trust, managed by chief administrative officers of the four organizations, outlined.

Kellogg Foundation has provided three-year grant of \$240,000.00; thereupon, it is anticipated Commission will be self-sustaining; primary purpose, to provide adequate and efficient hospital medical audits.

(19) Medical Audit Committee, ACS:

Dr. C. Wesley Eisele, official ACP representative; program supported by Kellogg Foundation and designed to supplement the work of the Commission on Professional and Hospital Activities, to assist hospital staffs to a better utilization of the information supplied by the basic statistical studies; full-time physician-director being sought.

(20) Study of Hospital Standards in Medicine:

Dr. Marion A. Blankenhorn, Director; Dr. Arthur R. Colwell, Chairman of Advisory Committee; informational report of progress presented; formal and final report to be made in April, 1957.

21 College members had surveyed 106 typical hospitals throughout the country; results being assembled; preliminary impressions indicate no simple valid yardstick available to measure quality of practice; principles of action were outlined.

Appropriation of \$37,000.00 by ACP will be expended by April, 1957; study continued from USPHS grant of \$43,100.00.

Dr. Blankenhorn will retire after the April meeting; Committee was seeking a successor.

(21) Fifth International Congress of Internal Medicine:

Dr. T. Grier Miller, President; first such Congress in United States at Philadelphia, April 24-26, 1958.

Details given concerning Executive Committee, raising of funds, program planning and administration; ACP to be one of the sponsors; Executive Secretary of the College would act in consulting capacity as Secretary-General; Dr. Wallace M. Yater, ACP Secretary-General, instructed to send formal letter of invitation to International Society of Internal Medicine; College appropriated \$3,000.00 toward expenses of the Congress.

(22) Committee on Educational Policy:

Dr. Howard P. Lewis, Chairman; report on procedure in selecting speakers for 1957 Annual Session program; summary proposal:

"There shall be a Program Committee composed of seven men, the President to be Chairman; members of the Committee would rotate, two men off each year; term of office, three years; committeemen should be selected from or very near medical centers in this country. The proposal contains detailed plan whereby solicitation of papers can be made, a plan whereby abstracts submitted will be sent out to the Committee members, inspected, graded and a certain stereotype of comment sent back to

the President, who would then segregate these papers according to their value and according to the structure that he may want to set up for his Annual Session. The President would bring these titles and abstracts to a meeting of the Committee in November, at which time a final selection would be made and where they would be placed on the program—General Sessions, Morning Lectures, Symposia, etc.

"Abstracts would first be submitted to the Secretary's Office, be duplicated and a copy sent to each committee member and to the President. The President shall have the final and complete say as to what the makeup of the program shall be in the end.

"The Committee also recommends that topics for the Panel Discussions and the TV Clinics should be in hand by November, so that overlapping and duplication can be avoided.

"The Committee on Educational Policy should have no connection with the Committee on Program, but rather should concern itself with a continuing study of the general structure of the College program and make such suggestions as is thought necessary from time to time.

"A Scientific Exhibit also was heavily favored by the survey made by our Committee, and while it would involve a great deal of work and expense and should not be competitive with the Scientific Exhibit of the AMA, it is recommended. The Committee believes there are certain subjects more adaptable to presentation by an exhibit than by other methods. There are things that really need three dimensional exhibition on technical sorts of things, such as instruments and techniques and other things that involve motion for demonstration. The Committee, therefore, favors a small Scientific Exhibit, possibly starting out with ten exhibits. These exhibits would be reserved strictly for those subjects best demonstrated by the exhibit method. We would exclude exhibits that are just a group of charts on the wall, or something like that. Should this trial prove successful and feasible, in the course of time the College might wish to expand the Scientific Exhibit to as many as fifteen. Our primary purpose would be merely to adopt a method of getting over something that cannot be presented satisfactorily in any other way. The exhibit should be conducted very much like that of the AMA; the College should furnish such facilities and assume such responsibility as does the AMA; exhibitors would be required to be present to demonstrate their exhibits throughout the meeting.

"The Scientific Exhibit might be conducted on an invitational basis, or on selection from proffered exhibits. The Program Committee might find in the course of studying the abstracts that some subject might be better adapted to an exhibit, and could propose that. The Scientific Exhibit should be under the jurisdiction of the President and the Program Committee."

RESOLVED, that the proposal presented for a Program Committee be adopted.

RESOLVED, that the College initiate a Scientific Exhibit in accordance with suggestions in the report.

(23) Treasurer's Report:

Dr. William D. Stroud, Treasurer, made a report on the investment portfolio, income from securities, average yield (3.86% on market value) and relationships with the investment counselors, Drexel & Co.

(24) Committee on Finance:

Dr. Herbert K. Detweiler, Chairman, covered all security transactions since previous meeting of Board, detailed operating statements for 1956, income and budget requirements for 1957, and other financial matters.

RESOLVED, that there be published in 1957 a Supplement to the 1955 Directory, rather than the publication of a complete and revised Directory, which would result in the saving of \$6,000.00, or more.

A budget for 1957, calling for estimated income of \$577,500.00 and expenditures of \$511,940.00, was formally passed.

(25) *Committee on Constitution and By-Laws:*

Dr. George F. Strong, Chairman. A very extended report, growing out of a four-hour meeting of the Committee, was presented, dealing with a revision of the By-Laws:

BY-LAWS, Article V, Add Paragraph (c) and Renumber Two Succeeding Paragraphs, (d) and (e)

- "(c) He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, and those holding official hospital and similar positions."

By resolution, this amendment was approved by the Regents, with provision for its submission to the Fellowship for action at the next Annual Business Meeting.

Much time was devoted to the consideration of aligning College Committees under headings of constitutional, standing and special committees. Inadequate time for consideration of proposed changes and standardizations led to the following resolution:

RESOLVED, that the proposals be approved in principle, but that they be re-submitted in full detail to the members of the Board of Regents at least two weeks prior to its next meeting in Boston.

(26) *Committee on Nominations:*

Dr. Eugene B. Ferris, Chairman. Report, presented by Dr. Philip S. Hench, restricted to a recommendation for reorganization of Committee on Nominations to provide continuity in the membership of the Committee, for the purpose of recording and passing on the advice and deliberations of one Committee to the next Committee.

RESOLVED, that in view of the present purpose to re-examine the status of all Committees, no specific action otherwise be taken, until the receipt of a final submitted draft from the Committee on Constitution and By-Laws shall have been received.

(27) *Executive Committee, Board of Governors:*

Dr. Carter Smith, Chairman. Recommendations submitted for substitution of a Reception and Cocktail Party, instead of a banquet, by the Governors to new Members at the Annual Session, with details for its operation.

Recommendation that no change be made in the By-Laws regarding the term of office of Governors.

Recommendation that newly elected Governors be brought to the autumn meeting of the Board of Regents and its Committees, for purposes of orientation.

Recommended that newly elected Governors be invited to an orientation "question and answer meeting" immediately after their election at the annual meeting site.

Expression of opinion that present schedule of fees and dues are satisfactory.

Submission of a vote of thanks to the Bauerlein Governors' Committee for its survey; recommendation that more effective means be initiated for making the College, its purposes and functions better known to physicians and the laity.

Recommendation that Dr. William C. Menninger accept responsibility for a plan of exchange of information among the Governors.

Recommendation that the Executive Committee appoint a Nominating Committee, to present nominees for the offices of Chairman and Vice Chairman.

All recommendations adopted formally by resolution.

RESOLVED, that the matter of traveling expenses of new Governors to the autumn meeting of the Regents and its Committees be referred to the Committee on Finance for consideration, recommendation and possible appropriation.

(28) *Committee on Public Relations:*

Dr. Fuller B. Bailey, Chairman. Dues of one Associate waived, due to incapacity; resignation of one Associate accepted; certain communications reviewed and appropriately disposed of.

(29) *Committee on Postgraduate Courses:*

Dr. Thomas M. McMillan, Chairman. Review of past courses and presentation of schedule of new courses for spring, 1957; report revealed continued success of the postgraduate program and a total registration for year 1956 in excess of 1,000.

(30) *Committee on Insurance:*

Dr. William C. Chaney, Chairman. A full review of the progress of the three Group Insurance Plans adopted by the College, with details of number of certificates in force, amount of benefits paid, and other relevant data; after three years' experience the Committee considered all the insurance plans on a sound and effective footing, well managed and with an excellent outlook for the future.

Recommendations included:

- (1) Plan to get more new subscribers;
- (2) More careful screening of applicants;
- (3) A careful screening of those claiming disability;
- (4) Assistance to the Insurance Administrators to contact ACP members readily when opportunity presents; encouragement to Governors to invite the Insurance Administrators to present a five-minute progress report at Regional Meetings

The distribution of a brief report from the Insurance Administrators three or four times annually to all members carrying the ACP insurance.

The report and recommendations were approved by resolution by the Regents.

(31) *Editor's Report:*

Dr. Maurice C. Pincoffs, Editor. Cumulative Index for first twenty years of ANNALS OF INTERNAL MEDICINE had been published; a limited number of Clinical Pathological Conferences will be published during coming year; number and average quality of submitted manuscripts are increasing and improving.

(32) *Committee on Revolving Residency Loan Fund:*

Dr. William D. Stroud, Chairman. 25 loans, amounting to \$22,700.00 had been made; balance available for future loans, \$17,300.00.

(33) *House Committee:*

Dr. William D. Stroud, Chairman. All improvements authorized at previous meeting of Board had been concluded in very acceptable manner; an illuminating lamp

recommended to be installed on the Stengel-Martin Portrait, with side lighting brackets removed.

Report also received on College property adjoining College Headquarters.

RESOLVED, that \$150.00 be appropriated for the removal of light brackets and installations of new lighting on the Stengel-Martin Portrait in the College Board Room.

(34) *American Council on Rheumatic Fever:*

Report by Dr. William D. Stroud on "commendable work being accomplished."

(35) *Editorial Board:*

Dr. Eugene B. Ferris, Chairman. A review in some detail on the editorial and business management of the ANNALS OF INTERNAL MEDICINE; discussion of elapsed time between receipt and publication of manuscripts; recommendation that the Cumulative Index of the ANNALS be published every ten consecutive Volumes; report, by resolution, approved.

(36) *American Board of Internal Medicine:*

Dr. Chester M. Jones, Chairman. A brief report dealing with current and future examination schedules; total certified to date by examination, 8,766; terms of members staggered, so that in future two men will retire each year from the twelve-man Board; Chairman will present a twenty-year report of the Board to the Regents in April, 1957.

Adjournment.

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

- Dr. Coyne Herbert Campbell, F.A.C.P., Oklahoma City, Okla., January 23, 1957
Dr. Frank Alexander Evans, F.A.C.P., Pittsburgh, Pa., December 13, 1956
Col. Augustus Benjamin Jones, Sr., (MC) USA, Retired, F.A.C.P., Palo Alto, Calif., November 5, 1956
Dr. William August Lange, F.A.C.P., Brooklyn, N. Y., February 2, 1957
Dr. Donald Luther Mahanna, F.A.C.P., Columbus, Ohio, November 19, 1956
Dr. Albert Bernard Siewers, F.A.C.P., Syracuse, N. Y., November 14, 1956
Dr. Clair Lazarus Stealy, F.A.C.P., San Diego, Calif., November 14, 1956
Dr. George Frederic Strong, F.A.C.P., Vancouver, B. C., Can., February 26, 1957
Dr. James Gurney Taylor, F.A.C.P., Milwaukee, Wis., November 30, 1956
Dr. Anna Weld, F.A.C.P., Rockford, Ill., December 2, 1956
Dr. Carl Vernon Weller, F.A.C.P., Ann Arbor, Mich., December 10, 1956

The College headquarters at 4200 Pine St., Philadelphia 4, Pa., would appreciate it if members and readers send in notices of the deaths of members promptly, so that suitable obituaries may be prepared and published. Frequently, deaths of members are not reported for several weeks or even months after a member is deceased.

DR. ROBERT LOUIS BENSON

Dr. Robert Louis Benson, F.A.C.P., died in Portland, Oregon, January 20, 1957 of a cerebral hemorrhage.

Dr. Benson was born in Flint, Michigan, May 30, 1880. On graduation from the Saginaw High School he attended the University of Michigan, obtaining his B.A. degree in 1904, and an M.A. degree two years later. He then took up the study of medicine at the University of Chicago, and received the degree of Doctor of Medicine in 1910. For two years after graduation he worked as bacteriologist with the Florida State Board of Health. In 1912, when reorganization of the University of Oregon Medical School was taking place, he came to the University as an assistant professor of anatomy. One year later he was made professor of pathology.

His academic career was interrupted in 1917 to enter the army. He joined Base Hospital 46, which was recruited from the staff of the University of Oregon Medical School, and was placed in charge of the laboratory services. During this time he was promoted from First Lieutenant to Major.

In 1919 he resumed his duties as professor of pathology at the University of Oregon Medical School and held this position for ten years. During this time he became interested in the field of allergy, and in 1929 resigned as head of the department to go into the practice of allergy. However, his affiliation with the school continued, first as assistant clinical professor of medicine from 1929 through 1937, and then as clinical professor of medicine from 1938 to 1952. He retired to emeritus status in 1952.

Dr. Benson was on the staffs of the U. S. Veterans, Providence and St. Vincent's Hospital, all in Portland. He was the author of many publications in the fields of pathology and allergy.

He was an enthusiastic gardener and devoted a great deal of time and attention to the cultivation of flowers and plants. He was particularly interested in the wild flowers of Oregon, and made many trips into the remote regions of the state in search of rare and unusual forms. His garden contained an amazing collection of Oregon wild flowers, and he had a constant stream of visitors from those interested in rare plants.

His professional societies included: The American Medical Association, the American Heart Association, the American Association for the Advancement of Science, The American Academy of Allergy, The Pacific Interurban Clinical Club, The North Pacific Society of Internal Medicine, The Portland Academy of Medicine and the City, County and State Medical Societies. His fellowship in the American College of Physicians dated back to 1932. He also held membership in Phi Beta Phi, Sigma Xi and Alpha Omega Alpha.

In 1933 the Governor of Oregon appointed Dr. Benson chairman of the Interim Committee for the Study of Public Health and Welfare. He was the president of the State Board of Health from 1935 to 1940, and for many years held membership in the State Public Welfare Commission (1934 to 1941) and the City of Portland Health Advisory Board (since 1934).

He married Hazel Altman of Portland on September 8, 1915. She survives him as do two daughters, Mrs. Nancy B. Drake, Portland, and Mrs. Ralph C. Altman, Los Angeles; a son, Robert L. Benson II, New York, and three grandchildren.

Dr. Benson left a host of friends who loved and admired him. It is with regret that the end of his long and useful life is recorded.

MERL L. MARGASON, M.D., F.A.C.P.,
Governor for Oregon

DR. CHARLES PALMER BONDURANT

Charles Palmer Bondurant, F.A.C.P., died suddenly at his home on October 23, 1956. He was born at Miami, Missouri on July 17, 1897, and attended Westminster College. He received his B.S. degree from the University of Missouri in 1922, and his M.D. degree from the University of Oklahoma in 1924. He interned at the University of Oklahoma Hospitals, and the Indianapolis City Hospital. He took graduate hospital work at the Skin and Cancer Hospital of New York City and postgraduate study at the University of London and the University of Vienna.

Dr. Bondurant's work was limited to dermatology and syphilology. In 1941 he became Professor of Dermatology and Syphilology at the University of Oklahoma School of Medicine. He was consulting dermatologist and syphilologist at the Federal Reformatory Hospital at El Reno, Oklahoma, and was attending dermatologist at St. Anthony's Hospital in Oklahoma City, Oklahoma.

Dr. Bondurant became a Fellow of the American College of Physicians in 1945, and was a Diplomat of the American Board of Dermatology and Syphilology. He was a member of the American Academy of Dermatology and Syphilology, the Southern Medical Association, the Oklahoma State Medical Association, the Oklahoma City Clinical Society and the Oklahoma State Dermatological Society. He was very active

in the work of the Oklahoma County Medical Society and the Oklahoma City Clinical Society, having served in offices of both organizations.

Survivors include his wife, Vera C. Bondurant, 253 N. W. 35th Street, and a daughter, Mrs. Joseph E. (Ann) Hathaway, of Cambridge, Massachusetts, and a son, Charles Palmer Bondurant, M.D., Resident in Dermatology at the University of Michigan Hospitals.

BERT F. KELTZ, M.D., F.A.C.P.,
Governor for Oklahoma

DR. HARRY ALFRED BRAY

Harry Alfred Bray, M.D., F.A.C.P., Saranac Lake, N. Y. Dr. Bray was born at Thorald, Canada on September 10, 1880. He received his doctorate in medicine from the University of Toronto in 1904 and interned at Lakeside Hospital, Cleveland, 1905-1906. Postgraduate work was pursued at the Royal Infirmary in Edinburgh, Scotland. He became a naturalized citizen of the United States in 1923. Academic posts included Lecturer in Tuberculosis at Cornell University Medical School, Associate Professor of Medicine at the Albany Medical College, and a member of the faculty of the Trudeau School of Tuberculosis. For many years Dr. Bray was Director of the Ray Brook State Tuberculosis Hospital and Associate Attending Physician at the Albany Hospital and a member of the consulting staff at the Municipal Sanitarium at Otisville, Physicians Hospital and Champlain Valley Hospital at Plattsburg. For many years he was a member of the Board of Directors of the General Hospital at Saranac Lake.

Medical societies included Fellowship in the American College of Physicians since 1948, a member of the American Medical Association, the American Trudeau Society, the American Clinical and Climatological Association, the Association for the Advancement of Science, the Franklin County Medical Society, Saranac Lake Medical Society and the New York State Medical Association. He was the author of a number of articles in medical journals. He did not retire until 1952 and died November 15, 1956, at the age of 76. He was unmarried.

Dr. Bray was largely responsible for making Ray Brook Hospital one of the finest tuberculosis institutions in the world. Its services and facilities benefited tremendously under his direction. He attracted a fine medical staff, encouraged research, developed the Department of Occupational Therapy and the Out-Patient Clinic and sponsored surgical treatment of tuberculosis. He was especially interested in training young doctors in the pursuit of research. His local newspaper characterized him as a "very perfect, gentle knight."

JOHN H. TALBOTT, M.D., F.A.C.P.,
Governor for Western New York

DR. COYNE HERBERT CAMPBELL

Dr. Coyne H. Campbell, a prominent psychiatrist, died suddenly on January 23, 1957. He was born at Davidson, Oklahoma on March 4, 1904.

Dr. Campbell obtained his B.S. degree from the University of Oklahoma in 1924, and his A.B. degree from the same university in 1925. He received his M.D. degree from Rush Medical College in 1928.

Dr. Campbell did special postgraduate work in neurology and psychiatry for a period of several years, including work at the Institute for Psychoanalysis at Columbia University.

Dr. Campbell became a Fellow of the American College of Physicians in 1939. He was also a member of the Oklahoma County Medical Society, the Oklahoma State Medical Association, the American Medical Association, Southern Medical Association, and the American Psychiatric Association. He was a Diplomate of the National Board of Medical Examiners and the American Board of Psychiatry and Neurology. He was Professor of Psychiatry and Neurology at the University of Oklahoma Medical School, and until the past two years had served for some time as Chairman of the Neuropsychiatry Department.

Many years ago he established a private sanitarium bearing his name, and a few years ago this was given to the Oklahoma Research Foundation, although he continued to direct the institution. Dr. Campbell is survived by his widow, Mrs. Margaret R. Campbell, and five daughters of 701 N. W. 15th Street, Oklahoma City, Oklahoma.

BERT F. KELTZ, M.D., F.A.C.P.,
Governor for Oklahoma

COL. AUGUSTUS BENJAMIN JONES, SR., MC, USA (RET.)

Dr. Augustus Benjamin Jones died November 5, 1956, in Palo Alto, California.

Dr. Jones was born at Fort McPherson, Georgia, August 5, 1889. He obtained his M.D. degree at the Atlanta College of Physicians and Surgeons in 1910 and served his internship at Grady Memorial Hospital in Atlanta. He entered the Medical Corps of the U. S. Army and was eventually advanced to the rank of Colonel. He filled many assignments in the Army in various parts of the United States and tours of duty in Hawaii and elsewhere. For the past ten years, prior to his death, he had been retired and was residing at his home in Palo Alto.

He was a member of the American Medical Association, a Fellow of the American Medical Association, a Fellow of the American College of Physicians since 1930, and was a Diplomate of the American Board of Internal Medicine. It is with regret that his loss is recorded.

STACY R. METTIER, M.D., F.A.C.P.,
Governor for Northern California

DR. ROBERT WOOD KEETON

Dr. Robert Wood Keeton died in Chicago, Ill., on January 22, 1957, from coronary artery disease.

Dr. Keeton was born in West Point, Miss., on July 7, 1883. He received his A.B. degree from Cumberland University in 1903, and from the University of Chicago in 1907. He obtained his M.D. degree from Northwestern University Medical School in 1916. In the early years of his professional life he taught and did investigative work in chemistry, physiology, and pharmacology at Northwestern University, and also the University of Illinois.

In 1920 he was appointed Assistant Professor of Medicine at the University of Illinois. In 1928 Dr. Keeton became Professor of Medicine and from 1934 to 1951 he was Chairman of the Department of Medicine at the University of Illinois.

He was Physician-in-Chief in the Research and Educational Hospitals. He was a consulting physician at St. Lukes, Henrotin, Illinois Central Hospitals, Chicago, and St. Francis Hospital, Evanston, Ill.

Dr. Keeton was the Chicago Secretary of the National Board of Medical Examiners from 1922 to 1935, and a member of that Board from 1938 on for many years. At the time of his death Dr. Keeton was President, Board of Directors, Suburban Cook County Tuberculosis Sanitarium District. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1941.

He was an active member in all the leading American medical societies devoted to internal medicine. He was a past President of the Chicago Society of Internal Medicine and a former Vice President of the Institute of Medicine of Chicago.

His life was devoted to the practice of internal medicine, teaching, and clinical investigation. His long experience in the basic sciences of medicine gave him a deep grasp of medical problems. He was a stimulating and effective teacher. At the time of his death he was still carrying on with his practice and on certain occasions he would put on a teaching performance that few people could equal. He kept his enthusiasm for teaching right to the end of his life. Here in Chicago, we will miss him from our ranks but the example of his great professional life will live on in the memories of those of us who knew him.

Surviving is his widow, Emily Keeton, 1500 Hinman Ave., Evanston, Ill.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. WILLIAM AUGUST LANGE

Dr. William August Lange died on February 2, 1957, in Brooklyn, New York of a heart attack.

Dr. Lange was born on December 10, 1900, in Brooklyn, New York. He received his B.S. and M.S. degree at the New York University and his degree of Doctor of Medicine at Cornell University Medical College in 1930. He was an intern at Methodist Hospital, (1930-32); Resident in Medicine at University Hospital, Syracuse, (1932-33).

He was an Instructor in Medicine at the Long Island College of Medicine, (1934-39); Instructor in Medicine to Nurses for many years at Methodist Hospital. He served continuously on the staff of the Methodist Hospital from 1933 to date, his last appointment that of Attending Physician.

He was a member of the following: Kings County Medical Society, New York State Medical Association, American Medical Association, Pan American Medical Association, Association of Military Surgeons of the United States, Brooklyn Society of Internal Medicine, American Heart Association and others. He had been a Fellow of the American College of Physicians since 1940; his specialty cardiology and pulmonary diseases.

Dr. Lange is survived by his widow, Mrs. Leila Lange, 610 Second Street, Brooklyn 15, New York. It is with sincere regret his loss is recorded.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. DONALD LUTHER MAHANNA

Dr. Donald Luther Mahanna died in the University Hospital, Columbus, Ohio, on November 19, 1956, from a cerebral vascular accident. Dr. Mahanna was born in Columbus, Ohio, November 6, 1911, receiving his A.B. degree in 1932 from West Virginia University. He completed his work for the Degree of Doctor of Medicine at Western Reserve University School of Medicine in 1936. His internship and residency training were accomplished at the University Hospital in Columbus, 1936 to 1939, following which he became a Junior Teaching Staff Member of the Ohio State University Medical Faculty. He advanced in responsibility and rank to Associate Clinical Professor of Medicine and Member of the Attending Staffs of the University, St. Francis, Mt. Carmel, and White Cross Hospitals, all in Columbus, Ohio. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1950.

During World War II, Dr. Mahanna held the rank of First Lieutenant in the Medical Corps. As a teacher he was admired and respected by students and faculty alike, and he commanded the affection and respect of his patients.

Dr. Mahanna was affiliated with many organizations. To these he contributed of his time and his unusual aptitude for sound planning and leadership. Dr. Mahanna had a precise mind and he was able to transfer this precision to the large and the complex groups that touched his life. At the time of his death, Dr. Mahanna was President of the Central Ohio Heart Association, having been one of the original founders and trustee. He was a member of the Board of the Ohio State Heart Association and the first President of the Columbus Internists Association.

He was President of the Watterson High School PTA and active in the Assumption Council, Knights of Columbus, and the Holy Name Society of the Immaculate Conception Church. He is survived by his widow, Mrs. Lucille G. Mahanna, and his four minor children.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. EDWARD CHARLES MASON

Dr. Edward Charles Mason, Professor of Physiology at the University of Oklahoma School of Medicine, died March 5, 1957 after a prolonged illness with liver disease.

Dr. Mason was born in Baltimore, Maryland in 1893 and received his A.B. degree from Drury College, Springfield, Missouri, in 1914. He obtained his M.D. and Ph.D. from the University of Cincinnati, Ohio, graduating from the College of Medicine in 1920.

He served as a Fellow at the Mayo Clinic in Rochester, Minnesota, in 1921 and 1922, and was added to the staff the following year. He became Associate Physiologist at the Henry Ford Hospital in Detroit, Michigan from 1923 to 1925 and became a member of the Physiology Department at the University of Oklahoma School of Medicine in 1928. He has been Professor for many years and until a few years ago served as Chairman of the Department.

Dr. Mason became a Fellow of the American College of Physicians in 1923. He was also a member of the American College of Cardiology, the American Geriatrics Society, and the American Association for the Advancement of Science. He was a member of the American Physiological Society, the Society of Experimental Biology and Medicine, Sigma Xi, Gamma Alpha, and the Phi Chi Medical Fraternity.

Dr. Mason is survived by his wife, Robbie Dee, of his home address, 1112 N. E. 16th, Oklahoma City; a daughter, Mrs. Mary Martha Mitchell of Vista, California; a son, Edward R. Mason, Key West, Florida; and a step-son, Billy D. Wade of Ada, Oklahoma.

BERT F. KELTZ, M.D., F.A.C.P.,
Governor for Oklahoma

CAPTAIN FRANK LESTER PLEADWELL, MC, USN (RET.)

Captain Frank Lester Pleadwell, Medical Corps, U. S. Navy, retired, age 83, died January 30, 1957, at the Tripler Army Hospital, Honolulu, Hawaii.

Born in Taunton, Massachusetts, on August 9, 1872, Captain Pleadwell attended the public schools of that city and was graduated from Harvard Medical School with the degree of Doctor of Medicine in 1896.

Captain Pleadwell was appointed Assistant Surgeon in the Medical Corps of the Navy from the State of Massachusetts and entered the Naval service on October 24, 1896. After completing more than 33 years active service, he retired from the Navy as a Captain in the Medical Corps on December 23, 1929.

His medals and decorations consisted of a bronze medal for service on board the *U.S.S. Nashville* during the Spanish-American War; the Spanish Campaign Badge for services in Cuba. He was recommended for the Navy Cross for meritorious service during World War I and received the Order of Commander of the Order of the British Empire, conferred by the British Government for services rendered during World War I.

Captain Pleadwell served with the Navy Medical Department throughout the United States and abroad and in ships of the Fleet. He is survived by his wife, Laura Pleadwell, 1522-C Alema Drive, Honolulu, T. H., and a daughter, Thedora Pleadwell.

Captain Pleadwell had been a Fellow of the American College of Physicians since 1923.

DR. J. GURNEY TAYLOR

Dr. J. Gurney Taylor, F.A.C.P., died on November 30, 1956, a few hours after concluding a routine day of clinical work in hospital and office. Death was due to rupture of an aneurysm of the abdominal aorta.

Dr. Taylor was born in Burlington, New Jersey, in 1872 and educated at Haverford College and the Medical School of The University of Pennsylvania, from which he was graduated in 1895. His clinical training was done at the Mercer Memorial House in Atlantic City, St. Christopher's Hospital for Children, and The University Hospital in Philadelphia with postgraduate study in cardiology and pediatrics in London. He entered clinical practice in Philadelphia in 1898 and in 1913 moved to Milwaukee where he established the clinical practice in which he was actively engaged at the time of his death. He served in the medical department of the United States Army from 1917 to 1919 and was retired with the rank of Lt. Colonel. During World War II he served on the Milwaukee Committee on Procurement and Assignment for Armed Services Personnel.

He had served as Chief of Staff of the Milwaukee Infants' Hospital, attending physician and member of The Executive Committee of the Milwaukee Children's

Hospital, Chief of Staff of the Johnston Emergency Hospital, attending physician and member of the governing staff of Columbia Hospital. In addition, he was a director of the medical alumni group of the University of Pennsylvania in Milwaukee and a past president of the Wisconsin University of Pennsylvania Alumni Club.

In addition to an active and distinguished career in the clinical practice of internal medicine and pediatrics, Dr. Taylor gave unstintingly of his time, energy, and ability to a large number of medical societies, many of which he served devotedly in positions of responsibility. He was a member of the American Climatological and Clinical Association, the Central State Pediatric Society which he served as president and member of the Executive Committee, Fellow of The American College of Pediatrics, Executive Committee of the National Board of Medical Examiners, National Anti-tuberculosis Association, Wisconsin Anti-tuberculosis Association, which he served as president for 11 years, as recording secretary for 12 years, and as director and executive board member for more than 20 years, Milwaukee Academy of Medicine, Milwaukee Society of Internal Medicine, Medical Milk Commission of Milwaukee which he served as secretary for many years, Wisconsin State Board of Medical Examiners, which he served as president for one term, Milwaukee County, State, and American Medical Association which he served as a member of the House of Delegates for 12 years and a member of the Council on Scientific Exhibits for 8 years. He was a Fellow of The American College of Physicians, 1927, and a Diplomate of the American Board of Internal Medicine.

The privilege of sixty years of active clinical practice and of "dying with his boots on" was richly deserved by Dr. Taylor in return for his deep devotion to his patients and his unselfish service to his profession. He was, likewise, deeply devoted to his family and friends to whom he has left the heritage of an unusually rich, full, and useful life. He is survived by his wife, Betty, his son, Dr. J. Gurney Taylor, Jr., F.A.C.P., and his daughter, Ann Richards Taylor.

FREDERICK W. MADISON, M.D., F.A.C.P.,
Governor for Wisconsin

DR. ALBERT WICKEN WALLACE

Albert Wicken Wallace, F.A.C.P., died unexpectedly of a cerebral hemorrhage on Dec. 25, 1956. He was born in Cleveland, Ohio on August 15, 1901. He received his Bachelor of Science and M.D. degrees at Western Reserve University, graduating in medicine in 1928. He served his internship at St. Luke's Hospital in Cleveland, Ohio. He practiced at Watkins Glen, New York and Miami Beach, Florida, before entering the Army during World War II. He was discharged as a Colonel at the Biloxi, Mississippi Air Force Base in 1946, and came to Tulsa, Oklahoma to become associated with the Springer Clinic staff. He remained associated with that clinic until his death.

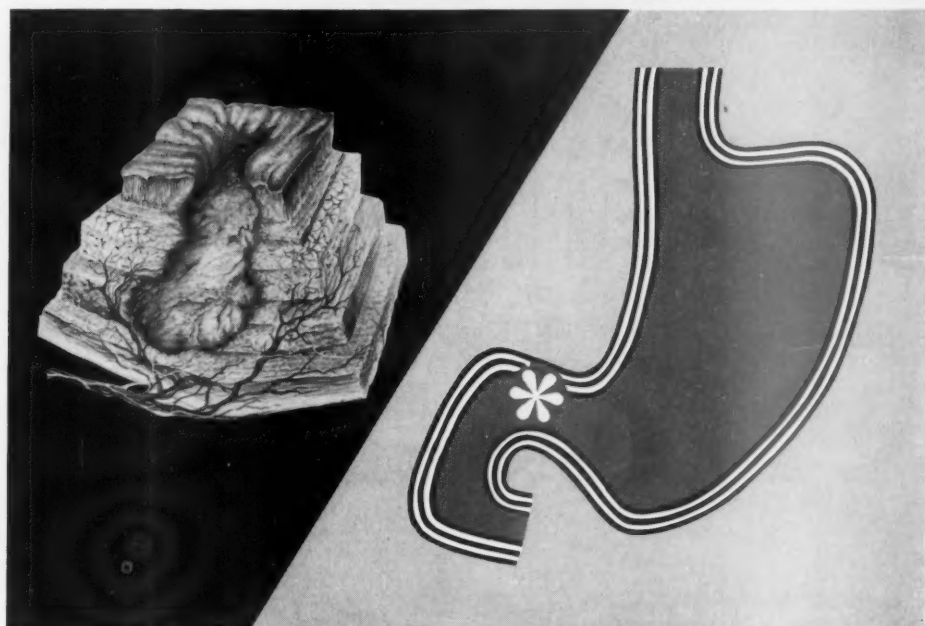
Dr. Wallace became a Fellow of the American College of Physicians in 1942. He was a member of the Tulsa County Medical Society, the Oklahoma State Medical Society and the American Medical Association. At the time of his death he was secretary-treasurer of the Oklahoma Diabetes Association and was president of the Tulsa Internist's Association. The family and friends of Dr. Wallace have established an annual memorial lectureship with the Tulsa Internist's Society.

Dr. Wallace's hobby was yachting, and he was currently Commodore of the Sequoyah Yacht Club.

Survivors include his widow, Edith Wallace, two daughters, Mrs. Mary Warner of Tulsa, Oklahoma, and Louise Wallace, a sophomore student at the University of Oklahoma. In addition, he is survived by two grandchildren and his parents, Mr. and Mrs. John E. Wallace, a brother and a sister, all of Cleveland, Ohio.

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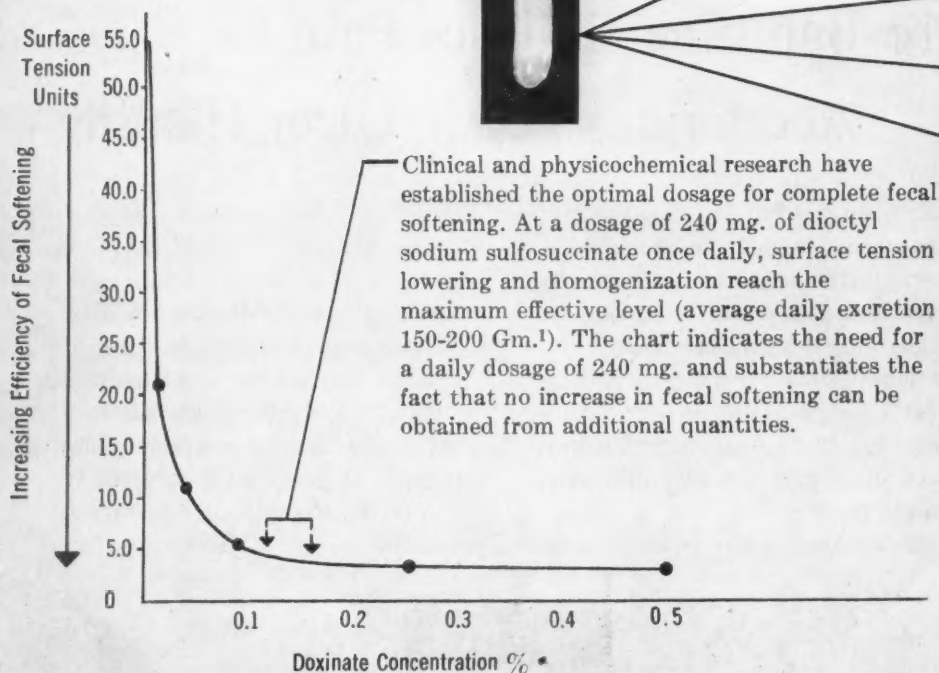
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1. Best & Taylor, The Physiological Basis of Medical Practice, 6th Ed.

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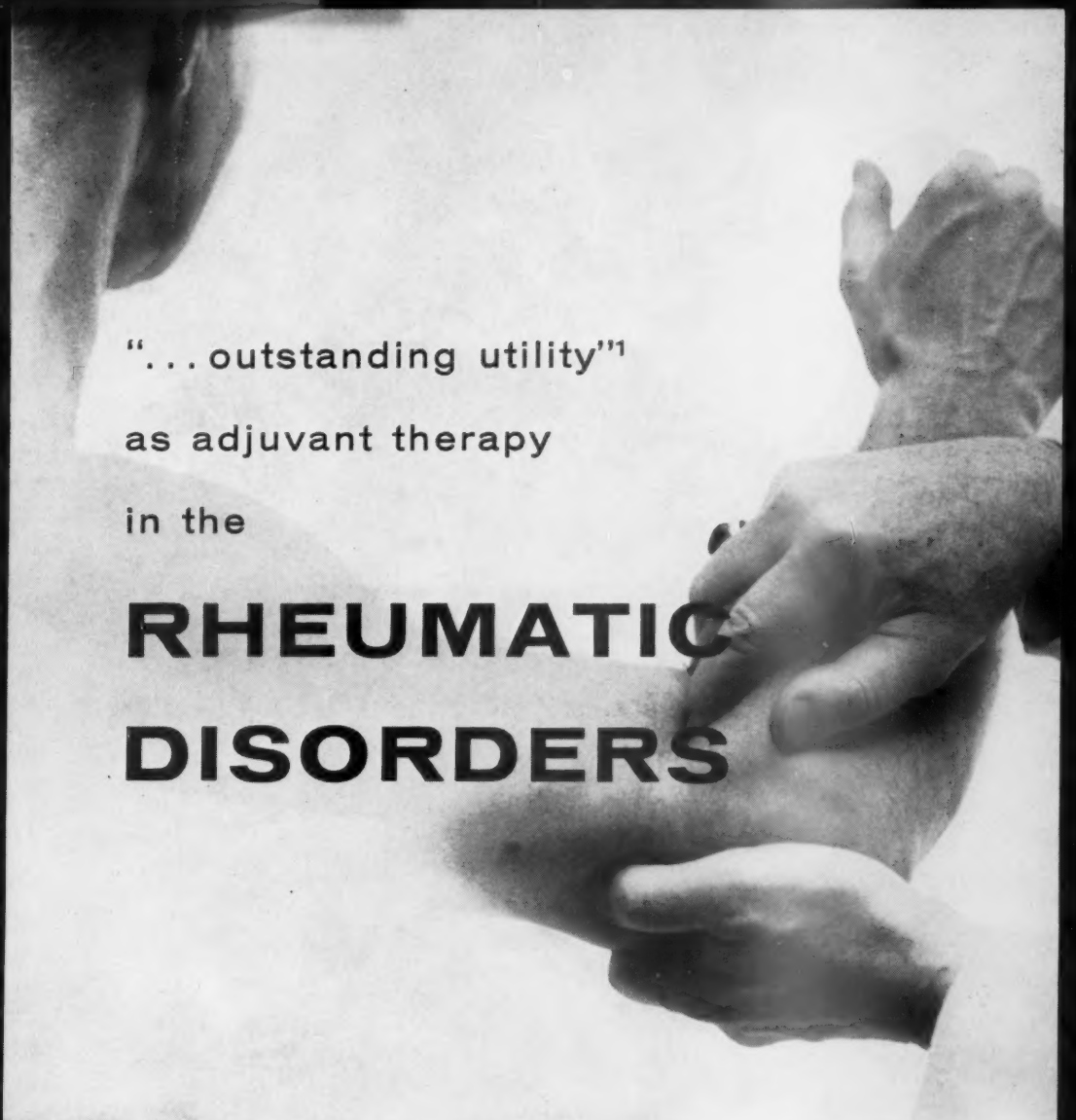
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1. Smith; R. T., et al.: Paper read before
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ing, A.M.A., June 13, 1956.



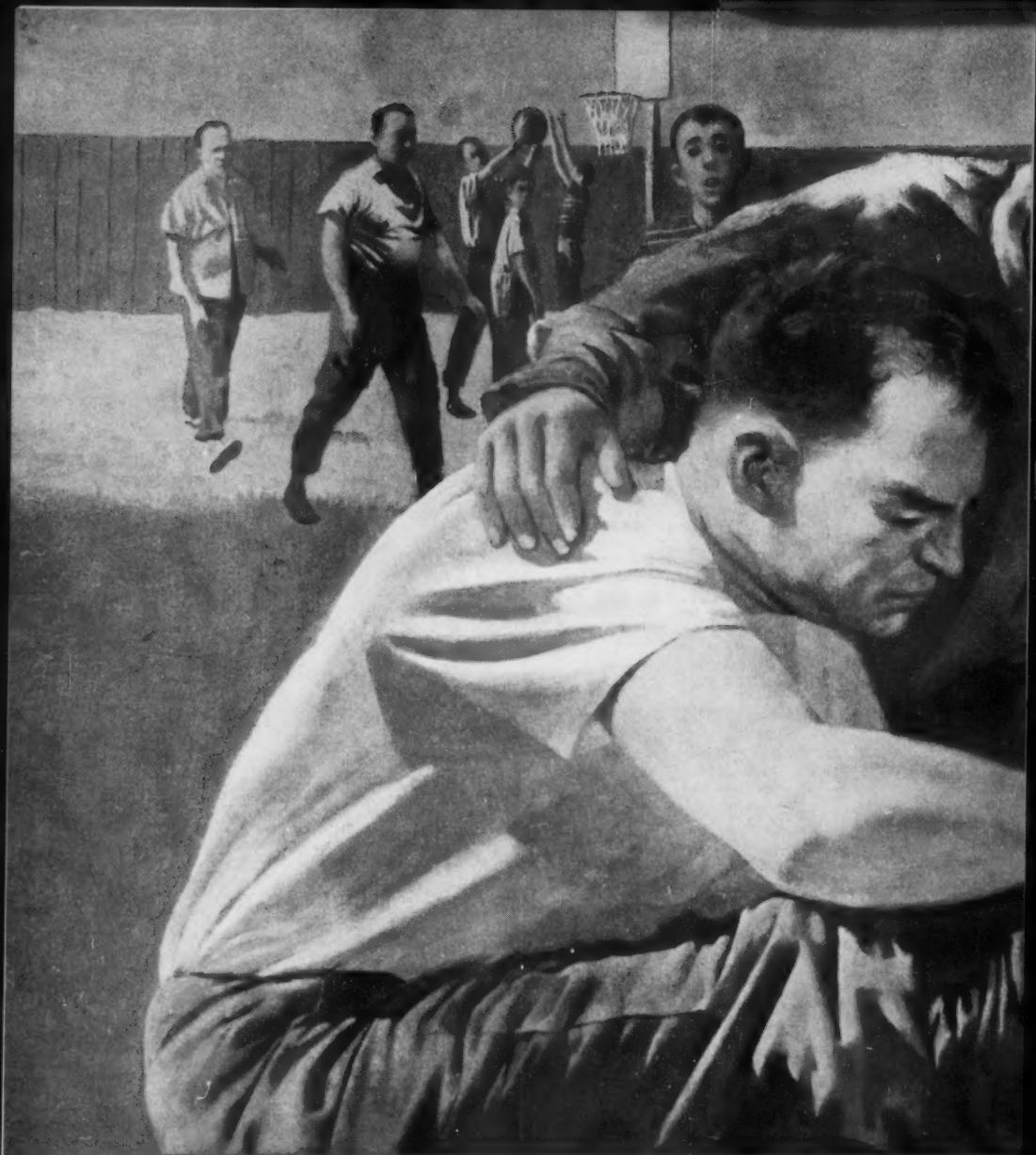
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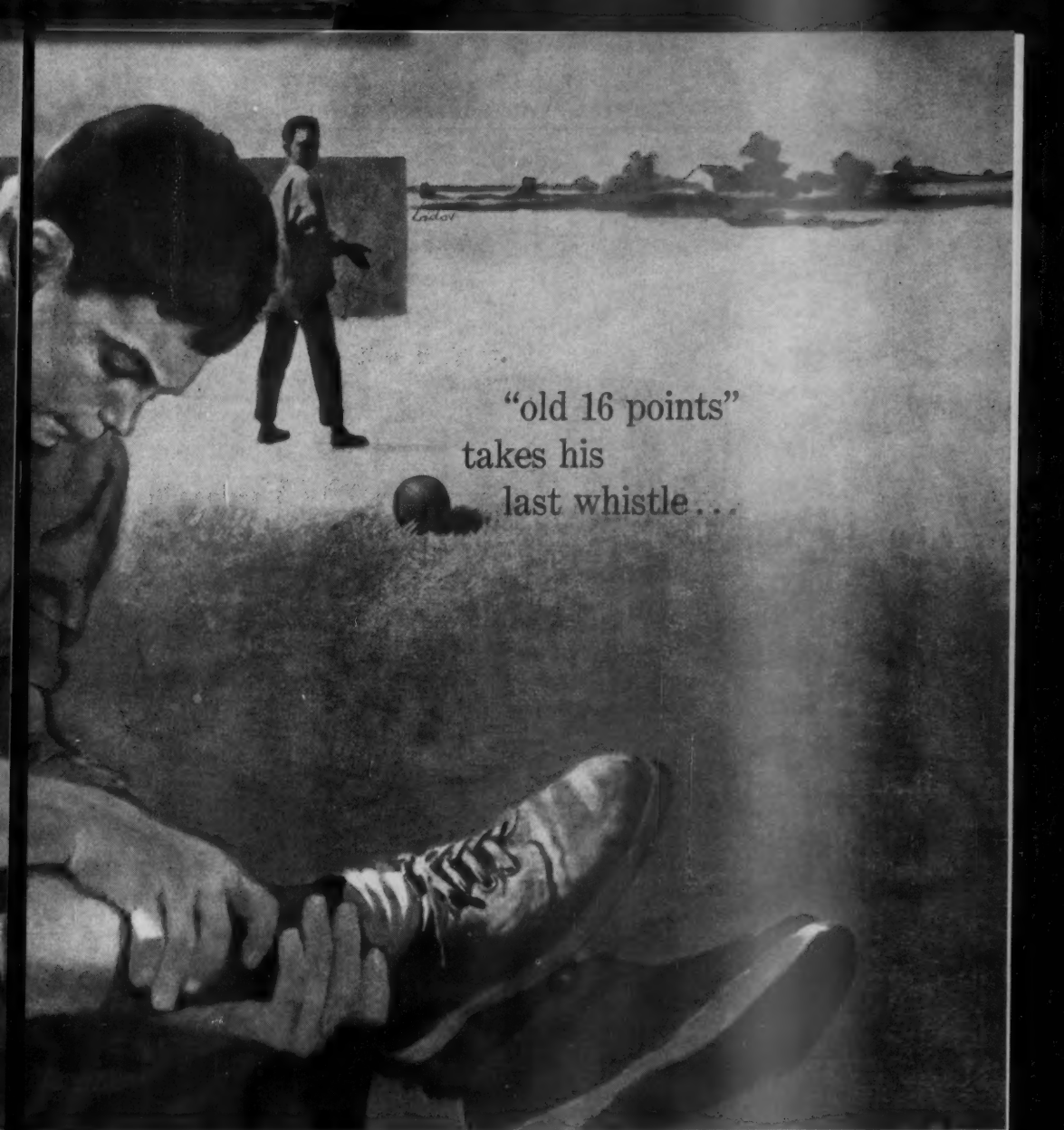
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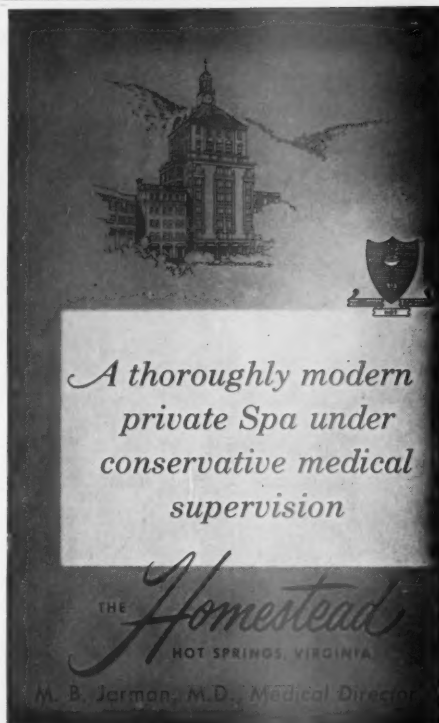
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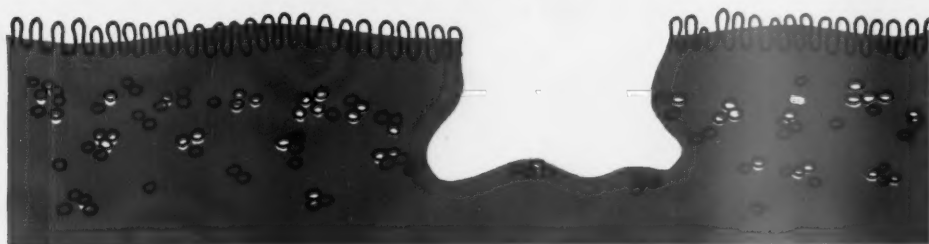
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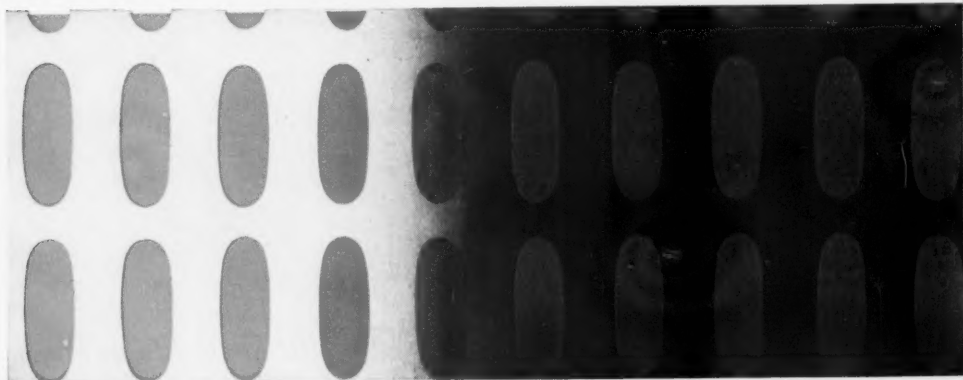
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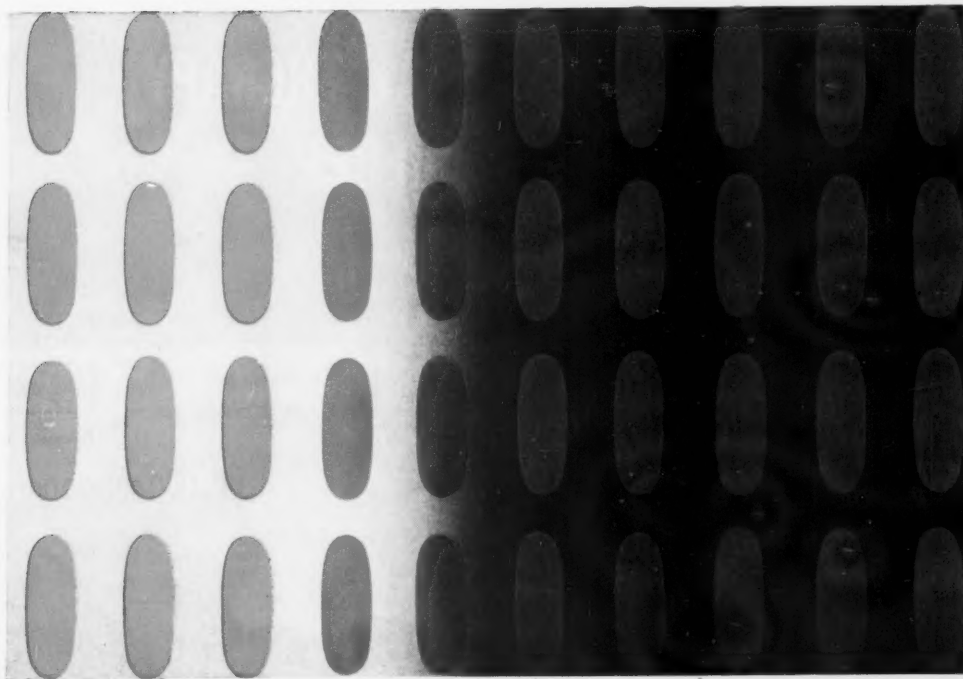




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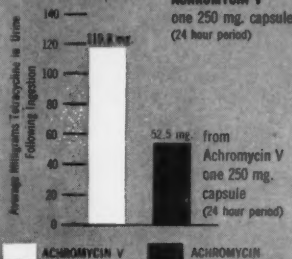
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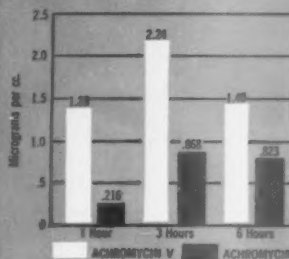
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*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, ed. 2, New York, The Blakiston Company, Inc., 1954, chap. 98, pp. 702, 703.

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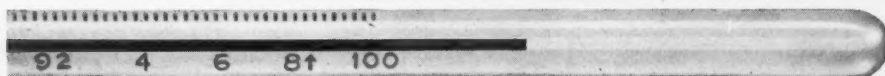
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(1) King, J. W., and Hainline, A., Jr.: Commercial Glucose Oxidase Preparations for the Detection of Glucose in Urine, *Cleveland Clin. Quart.* 23:212, 1956. (2) Leonards, J. R.: Evaluation of Enzyme Tests for Urinary Glucose, *J.A.M.A.* 163:260 (Jan. 26) 1957.

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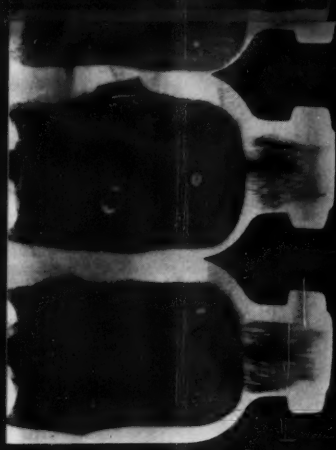
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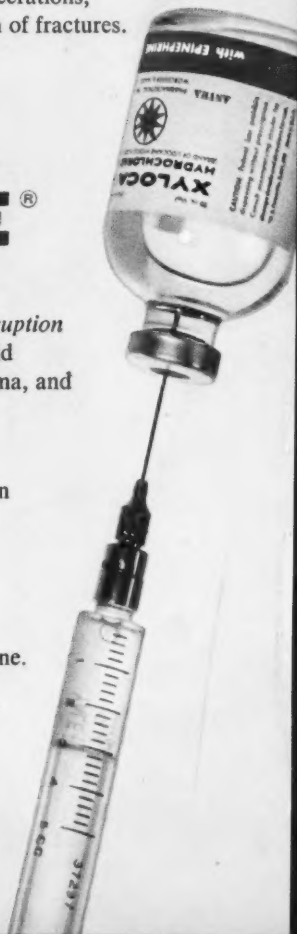
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*Southworth, J. L., and Dabbs, C. H.: Xylocaine: a superior agent for conduction anesthesia, *Anesth. & Analg.* 32:159 (May-June) 1953.

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Sokoloff, O. J.: A.M.A. Arch. Dermat. 74: 293, 1956.

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Thymann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. 17: 19, 1956.

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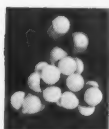
Boruss, J.C.: J.A.M.A. 157: 1596, 1955.

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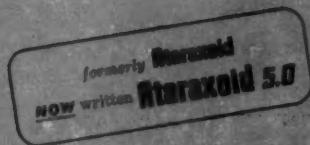
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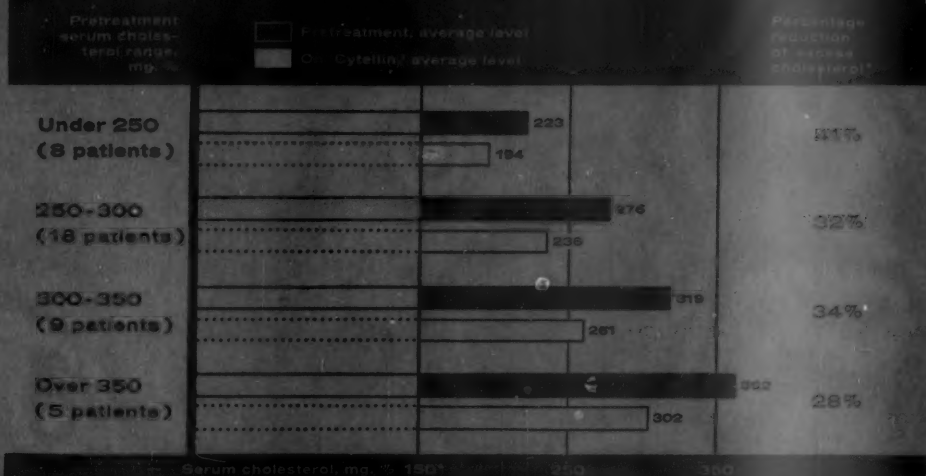
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COMBINATION TABLETS

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*Although a "normal" serum cholesterol level has not been established, a concentration of 150 mg. per cent is widely approximated the "usual" level. Concentrations above this are considered excess.

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